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Award Number: W81XWH-04-C-0569

TITLE: Selection Criteria and Prioritization of Resuscitation Fluid Adjuvants

PRINCIPAL INVESTIGATOR: Michael Falk, Ph.D.

CONTRACTING ORGANIZATION: Life Science Research Office
Bethesda, MD 20814-3998

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TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE

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6. AUTHOR(S) Michael Falk, Ph.D. E-mail: falkm@lsro.org			5d. PROJECT NUMBER					
					5e. TASK NUMBER			
					5f. WORK UNIT NUMBER			
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13. SUPPLEMENTARY NOTES								
14. ABSTRACT PURPOSE To provide the sponsor with advice on criteria useful for evaluating potential technologies/products for resuscitation fluid for use by first-responders in combat. LSRO was also tasked with prioritizing pre-proposals and full proposals most warranting an investment in Sponsor resources. SCOPE The Phase 1 review of pre-proposals included those received in response to a public call for information on the topic of resuscitation fluids or components of fluids or adjuvant therapies and excluded equipment such as infusion and monitoring devices. Reviews were to include consideration of the military relevance of the product, the stage of product development, and the scientific merits of the investigation. In Phase 2, processes and forms currently in use by the military and other federal programs for the review of scientific research were examined with an eye towards improvements that would yield the type of data and information necessary for future expert reviews. The Phase 3 review of full proposals was limited to 12 received in response to 16 invitations (<i>i.e.</i> , the highest ranking pre-proposals). MAJOR FINDINGS Phases 1 and 2: Of the 10 clinical pre-proposals reviewed, the expert panel identified 2 leading candidates. Of the 49 preclinical pre-proposals reviewed, the expert panel identified 5 top-tier pre-proposals and 9 second-tier pre-proposals. Phase 3: The review of 12 full proposals yielded 5 high ranking experimental products, most of which are likely to be ready for clinical testing by 2008. SIGNIFICANCE Development of one or more of the highest ranking novel strategies to treat hemorrhagic shock may improve effectiveness of resuscitation fluids, reducing the number of military casualties who are killed-in-action. Furthermore, the LSRO expert panel developed new proposal forms, that improved the quality, relevance, and organization of information provided for review of proposals beyond that provided by earlier instructions. The new forms are available to the Sponsor for use in future proposal reviews.								
15. SUBJECT TERMS Resuscitation fluid, hemorrhage, shock, survival, product development, grant								
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 170	19a. NAME OF RESPONSIBLE PERSON USAMRMC			
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)			

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INTRODUCTION

The U.S. Army Medical Research and Materiel Command (USAMRMC) and the Office of Naval Research (ONR) are seeking novel treatments to resuscitate wounded combatants. Depending on terrain, weather, and military situation, U.S. soldiers and marines wounded in combat may have to endure a prolonged period of time before evacuation to surgical care. On the battlefield, combatants who are bleeding sufficiently to compromise perfusion of vital organs require immediate medical care by a medic or combat lifesaver. Resuscitation fluid to replace lost blood volume is carried in limited supply. Products are needed that are practical to transport and use on the battlefield and which are effective in increasing survival and decreasing adverse complications of exsanguinating hemorrhage during and after prolonged evacuation.

The purpose of this project was to provide the sponsor with advice on criteria useful for evaluating potential technologies/products for resuscitation fluid for use by first-responders in combat and to prioritize pre-proposals and full proposals most warranting an investment in Sponsor resources.

BODY

The AFRRF project was divided into three phases:

- Phase 1: Establish criteria and review of pre-proposals. Pre-proposals were received in response to a public call for information on the topic of resuscitation fluids or components of fluids or adjuvant therapies and excluded equipment such as infusion and monitoring devices. Reviews included consideration of the military relevance of the product, the stage of product development, and the scientific merits of the investigation.
- Phase 2: Improve processes and forms. Forms currently in use by the military and other federal programs for the review of scientific research were examined. Improvements were made with an eye towards obtaining and organizing the type data and information necessary for future expert reviews.
- Phase 3: Review of full proposals. Proposals were limited to 12 received in response to 16 invitations (*i.e.*, the highest ranking pre-proposals).

Specific aspects of the project, particularly the development of criteria and methods to evaluate proposed investigations, are described in detail in the report, attached as an appendix.

List of Personnel

The following individuals received a portion of their salary from this research effort:

- Michael C. Falk
- Robin Feldman
- Karin French
- Rebecca Johnson
- Catherine J. Klein
- Shelia McGreger

KEY RESEARCH ACCOMPLISHMENTS

- Phase 1: Of the ten *clinical* pre-proposals reviewed, the expert panel identified two leading candidates. Of the 49 *preclinical* pre-proposals reviewed, the expert panel identified a group of

five top-tier pre-proposals and a group of nine second-tier pre-proposals. The Sponsor invited these 16 organizations to submit full proposals for review.

- **Phase 2:** The LSRO expert panel developed new proposal forms, that improved the quality, relevance, and organization of information provided for review beyond that provided by earlier instructions. The new forms are available to the Sponsor for use in future proposal reviews.
- **Phase 3:** The review of 12 full proposals yielded 5 high ranking experimental products, most of which are likely to be ready for clinical testing by 2008 and have the potential to substantially improve survival from traumatic hemorrhage in combat. An additional three mid-tier candidates had sufficient scientific merit to fund.

REPORTABLE OUTCOMES

Several of the full proposals ranked highest by the LSRO expert panel are scheduled to be funded by the Army in early 2006.

CONCLUSIONS

Development of one or more of the highest ranking novel strategies to treat hemorrhagic shock may lead to improved effectiveness of resuscitation fluids, reducing the number of military casualties who are killed-in-action.

REFERENCES

Bibliography of Project Publications and Presentations

1. Life Sciences Research Office (2005) *Recommendations for Reviewing Research on Advanced First-Responder Resuscitation Fluids and Adjunct Therapies*. (Klein, C. J., ed.). Bethesda, MD: Life Sciences Research Office, Inc. ISBN: 0-9753167-5-3; Library of Congress Catalog Number: 2005929910. [Phase 1 and 2 report; See Appendix]
2. Klein C, Prough D, Boucher B, French K, Falk M. (2005) P32. Novel fluids for resuscitation of hemorrhagic shock on the battlefield. Shock 23 (Suppl 3):27. 28th Annual Meeting, Shock Society, Marco Island, FL June 4-8, 2005. [poster]
3. Klein CJ, Falk MC. (2005) P-58. Novel fluids for resuscitation of hemorrhagic shock on the battlefield. Artificial Cells, Blood Substitutes, and Biotechnology. (Suppl):165 [*in press*]. Xth International Symposium on Blood Substitutes, Providence, RI June 12-15, 2005. [poster]

Other Project Materials

- Proposal forms and instructions developed in the course of this project are included in Appendix B. These are available for use by the Sponsor in future proposal reviews. The forms and instructions in Appendix B are updated from earlier versions that were published in the July 2005 report, *Recommendations for Reviewing Research on Advanced First-Responder Resuscitation Fluids and Adjunct Therapies*.
- Non-proprietary portions of presentations made at project meetings by Army representatives and others are available to the public free-of-charge by accessing the project website: [http://www.lsro.org/resusc\(frames_resusc_meetings.html](http://www.lsro.org/resusc(frames_resusc_meetings.html)
- LSRO prepared critiques summarizing the merits and limitations of each pre-proposal and proposal. These were submitted to the Sponsor along with data tables of individual pre-proposal and proposal scores and rankings.

APPENDIX A: ABSTRACTS OF POSTER PRESENTATIONS

- A.1 Novel Fluids for Resuscitation of Hemorrhagic Shock on the Battlefield (June 4-8, 2005)
A.2 Novel Fluids for Resuscitation of Hemorrhagic Shock on the Battlefield (June 12-15, 2005)

(A.1) Reference: Klein C, Prough D, Boucher B, French K, Falk M. (2005) P32. Novel fluids for resuscitation of hemorrhagic shock on the battlefield. Shock 23 (Suppl 3):27. 28th Annual Meeting, Shock Society, Marco Island, FL June 4-8, 2005. [poster]

NOVEL FLUIDS FOR RESUSCITATION OF HEMORRHAGIC SHOCK ON THE BATTLEFIELD. C. Klein*, D. Prough*, B. Boucher*, K. French*, M. Falk.* (Spon: K. Burhop) Life Sciences Research Office, Bethesda, MD 20814.

Objective: A survey was conducted to identify strategies under development for use as resuscitation fluid that potentially might reduce complications and improve chances for survival from hemorrhagic shock. Of particular interest are strategies that can be utilized by combat medics on the battlefield.

Methods: Information on novel resuscitation fluids was supplied by more than 50 researchers in response to a public call for information by the U.S. Army Medical Research and Materiel Command and in response to direct invitation by the Life Sciences Research Office. The survey was conducted in association with an expert panel assembled to review and prioritize proposed treatment regimens and develop a framework for future scientific reviews. Provisions were made to review but not reveal proprietary data by executing confidentiality agreements.

Results: Several parallel approaches are under consideration for resuscitation fluid that include one or more of the following strategies: improve oxygen delivery (e.g., hemoglobin-based oxygen carriers); support metabolism (e.g., ethyl pyruvate); favorably alter rheology and coagulation (e.g., lyophilized platelets); promote cardiovascular stability; and modulate immune response (e.g., human recombinant interleukin-6). More than 20 researchers proposed measuring markers of inflammation and immune function to assess effects of resuscitation fluid treatment.

Conclusion: Development of one or more of these novel strategies to treat hemorrhagic shock may lead to improved effectiveness of resuscitation fluids, earlier after the wounding event, reducing the number of military casualties who are killed-in-action.

Project funded by the U.S. Army Medical Research and Materiel Command and the U.S. Office of Naval Research.

(A.2) Reference:

Klein CJ, Falk MC. (2005) P-58. Novel fluids for resuscitation of hemorrhagic shock on the battlefield. Artificial Cells, Blood Substitutes, and Biotechnology. (Suppl):165. Xth International Symposium on Blood Substitutes, Providence, RI June 12-15, 2005. [poster]

NOVEL FLUIDS FOR RESUSCITATION OF HEMORRHAGIC SHOCK ON THE BATTLEFIELD

C. J. Klein and M. C. Falk

Life Sciences Research Office, Bethesda, MD 20814

Objective: A survey was conducted to identify strategies under development for use as resuscitation fluid that potentially might reduce complications and improve survival from hemorrhagic shock. Of particular interest were strategies that could be utilized by combat medics on the battlefield.

Methods: Information on novel resuscitation fluids was supplied by more than 50 researchers in response to a public call for information and in response to direct invitation by the Life Sciences Research Office. The survey was conducted in association with an expert panel assembled to review and prioritize proposed treatment regimens and develop a framework for future scientific reviews. Provisions were made to review but not reveal proprietary data by executing confidentiality agreements. **Results:** Several parallel approaches are under consideration for resuscitation fluid that include one or more of the following strategies: improve oxygen delivery (e.g., hemoglobin-based oxygen carriers); support metabolism (e.g., ethyl pyruvate); favorably alter rheology and coagulation (e.g., lyophilized platelets); promote cardiovascular stability; and modulate immune response (e.g., human recombinant interleukin-6). **Conclusion:** Development of one or more of these novel strategies to treat hemorrhagic shock may lead to improved effectiveness of resuscitation fluids, earlier after the wounding event, reducing the number of military casualties who are killed-in-action. Project funded by the U.S. Army Medical Research and Materiel Command and the U.S. Office of Naval Research.

APPENDIX B: PROPOSAL FORMS AND INSTRUCTIONS
(an interactive version of forms for actual use is available from LSRO)

United States Army Medical Research and Materiel Command

RESEARCH PROPOSAL COVER PAGEThis is a: Preproposal Full Proposal1. PROPOSAL TITLE (*Do not exceed 120 characters, including spaces and punctuation.*)

Supplement to USAMRMC BAA 04-1: Candidate Technologies for Advanced First-Responder Resuscitation Fluid (AFRRF). Funding Opportunity Number: W81XWY-BAA-AFRRF. If a preproposal was previously submitted, enter USAMRMC Log No: and Previous Preproposal Title:

3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR (*name of Offeror*)

3a. NAME (<i>Last, first, middle</i>)		3b. DEGREE(S)		
3c. POSITION TITLE		3d. MAILING ADDRESS		
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT				
3f. MAJOR SUBDIVISION				
3g. TELEPHONE AND FAX (<i>Area code, number and extension</i>) Tel: _____ FAX: _____		E-Mail (<i>Not website URL</i>): _____		
4. HUMAN SUBJECTS RESEARCH: <input type="checkbox"/> No <input type="checkbox"/> Yes	4a. Human subjects assurance number:		5a. USE OF VERTEBRATE ANIMALS <input type="checkbox"/> No <input type="checkbox"/> Yes	
	4b. Clinical Trial: <input type="checkbox"/> No <input type="checkbox"/> Yes	4c. Phase III Clinical Trial: <input type="checkbox"/> No <input type="checkbox"/> Yes	5b. IACUC approval date / /	
6a. PROPOSED PERIOD OF SUPPORT (MM/DD/YY)		7. ESTIMATED COSTS FOR INITIAL 12-MONTH BUDGET PERIOD	8. ESTIMATED TOTAL COSTS FOR PROPOSED PERIOD OF SUPPORT	
Earliest start date / /	Duration in years	7a. Direct Costs (\$)	7b. Total Costs (\$)	8a. Direct Costs (\$)
6b. Proposal valid until: / /		9a. APPLICANT ORGANIZATION (PI's organization):		
10. AUTHORIZED REPRESENTATIVE SIGNING FOR APPLICANT ORGANIZATION		9b. DUNS Number: _____		
Name: Title: Mailing Address:	Tel: FAX: E-mail:			
11. ALTERNATE PRINCIPAL INVESTIGATOR Name: Tel: E-Mail:		12. ALTERNATE REPRESENTATIVE FOR ORGANIZATION Name: Tel: E-Mail:		
13. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.		SIGNATURE OF PI/PD NAMED IN ITEM 3a. ("For" and "Per" signatures not acceptable.)		DATE / /
14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with US Army Medical Research Acquisition Activity terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.		SIGNATURE OF OFFICIAL NAMED IN ITEM 10. ("Per" signatures not acceptable.)		DATE / /

NOTHING ON THIS PAGE IS PROPRIETARY INFORMATION

Principal Investigator/Program Director (Last, First, Middle):

PROPOSAL TITLE (*Do not exceed 120 characters*):

Keywords (6-8 words):

ABSTRACT: State the proposal's broad, long-term objectives and specific aims, making reference to the relevance of the project to hemorrhagic shock. Identify the product or agent to be tested. Describe concisely the research hypothesis, design, and main methods for achieving these goals. Describe the primary data to be collected. State what is innovative about your approach.

In addition, in two or three sentences, describe in plain, lay language the relevance of this research to combat casualty care. If the proposal is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information.

DO NOT EXCEED THE SPACE PROVIDED (about 200 words):

6.25" x 6.5"

NOTHING ON THIS PAGE IS PROPRIETARY INFORMATION

Principal Investigator/Program Director (Last, First, Middle):

PERFORMANCE SITE(S) OF PROPOSED RESEARCH (organization, city, state):

KEY PERSONNEL. Start with Principal Investigator. List all other key personnel in alphabetical order. *Use continuation pages as needed to provide the required information in the format shown below.*

Name (Last, First Middle)	Organization	Role on Project
---------------------------	--------------	-----------------

OTHER SIGNIFICANT CONTRIBUTORS

Name (Last, First Middle)	Organization	Role on Project
---------------------------	--------------	-----------------

Principal Investigator/Program Director (Last, First, Middle):

The name of the principal investigator/program director must be provided at the top of each printed page and each continuation page.

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Product/Agent (Form E)	_____
Military Relevance of Project/Agent (Form F)	_____
Research Plan/Body of Proposal (Form G).....	_____
Specific Aims	_____
Background and Significance	_____
Preliminary Data	_____
Research Design and Methods	_____
Research Bibliography	_____
Acronym/Symbol Definition	_____
Detailed Cost Estimate for Initial 12 Month Budget Period (Form H)	_____
Summary Budget for Entire Proposed Period of Support (Form I).....	_____
Budgets Pertaining to Consortium/Subaward Contractual Arrangements	_____
Biographical Sketch (Form J)– Principal Investigator/Program Director	_____
Other Biographical Sketches (Form J)	_____
Existing/Pending Support and Past Related Efforts	_____
Consortium/Contractual Arrangements for Proposed Research	_____
Letters Confirming Collaboration (<i>Full proposals only</i>)	_____
Available Facilities and Major Equipment (Form K)	_____
Institution Safety Program Plan (<i>Full proposals only</i>)	_____
Certificate of Environmental Compliance (<i>Full proposals only</i>)	_____
Human Use Required Information and Approval (<i>Full proposals only</i>)	_____
Animal Use Required Information and Approval (<i>Full proposals only</i>)	_____
Appendix (<i>Full proposals only. No page numbering necessary for Appendix</i>)	_____
	<input type="checkbox"/> Check if Appendix is included

Other items (list):

Principal Investigator/Program Director (Last, First, Middle):

STATEMENT OF WORK

The Statement of Work (SOW) outlines performance expectations for the project within the timeframe of the budget period. List the major performance goals of the proposed research. In a series of short statements, outline the approach that will be taken to achieve these goals. Include specific tasks, systems, and materials that are reasonable estimates for testing the proposed hypotheses of the study. For each year of the contracted project, define the milestones and goals that the principle investigator/applicant organization is expected to meet. The SOW might be incorporated into the award document and, as such, is subject to release under FOIA. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED ONE PAGE.**

NOTHING ON THIS PAGE IS PROPRIETARY INFORMATION

Product/Agent
Do not exceed a total of 2 pages for Form E including the continuation page if needed for full proposals or 1 page for preproposals. The citations for publications referred to on Form E should be listed in the Research Bibliography.
PRODUCT IDENTITY (and formulation):
PRODUCT CHARACTERIZATION Physicochemical properties (e.g., potency, long-term stability, temperature for storage/transport, solubility, stability after reconstitution):
Pharmacokinetics (bioavailability/absorption, distribution, half-life, metabolism, clearance/excretion):
ADMINISTRATION (route, preparation, volume per unit dose):
SAFETY DATA (brief overview):
PHARMACODYNAMICS AND MECHANISM OF ACTION (for treatment of exsanguinating hemorrhage, e.g., volume expander):
PROVIDE A TIMELINE OF PRODUCT DEVELOPMENT (from current stage to first/next clinical phase): Is product/agent currently in U.S. market? No <input type="checkbox"/> Yes <input type="checkbox"/> If yes, by what route of administration and for what indication(s)? If no, does product/agent have investigational new drug (IND) status for any indication?
PRODUCT MANUFACTURER: Letter of support from corporate partner included in this proposal (<i>Full proposals only</i>): No <input type="checkbox"/> Estimated cost range per dose:
INTELLECTUAL PROPERTY PROTECTION RIGHTS/CONTRACTS (e.g. patents):
OUTLINE PROCESS FOR COMMERCIAL DEVELOPMENT: Is the product/agent sufficiently attractive to industry that it will be commercially viable outside the military environment? What is the plan for taking the product/agent to market?

Principal Investigator/Program Director (Last, First, Middle):

Military Relevance of Product/Agent

Assess the strengths and limitations of use of the product/agent by Combat Casualty Care compared to military product "requirements." Consider first-responder transport, preparation, and safe administration of product. How will they select the patients to whom it should be administered? Does this approach (1) increase the probability of survival from exsanguinating hemorrhage on the battlefield and/or (2) decrease later medical complications? Do not exceed 1 page for Form F. Citations should be listed in the Research Bibliography section of the proposal.

Principal Investigator/Program Director (Last, First, Middle):

Research Plan

Do not exceed 8 pages for full proposals or 4 pages for preproposals. All tables, graphs, figures, diagrams, and charts must be included within the page limit.

The citations for publications referred to in the Research Plan should be listed in the Research Bibliography.

Specific Aims, Background and Significance (*Do not exceed 2 pages for full proposals or 1 page for preproposals*)

Specific Aims and Hypothesis:

Background and Significance: Discuss the proposed mechanism of action of the experimental product/agent for use in resuscitation therapy and the relevance of the project to the treatment of hemorrhagic shock under combat conditions. How is this approach innovative?

Preliminary Data (*Do not exceed 2 pages for full proposals or 1 page for preproposals*) Demonstrate that the product can be administered under the circumstances proposed.

Research Design and Methods (*Do not exceed 4 pages for full proposals or 2 pages for preproposals*) Describe the research design and methods in sufficient detail for evaluation. Specify the type and number of subjects and how the data will be collected. Define the measurements, end points and the statistical protocols and analysis.

Protection of Human Subjects:

Data and Safety Monitoring Plan:

Use of Vertebrate Animals: Discuss how this model is relevant to hemorrhagic shock under combat

Provide a timetable for the proposed project:

Principal Investigator/Program Director (Last, First, Middle):

DETAILED COST ESTIMATE FOR INITIAL 12 MONTH BUDGET PERIOD					FROM	THROUGH	
PERSONNEL (<i>Applicant organization only</i>)		TYPE APPT. (months)	Institutional Annual Base Salary	% EFFORT ON PROJECT	DOLLAR AMOUNT REQUESTED (<i>omit cents</i>)		
NAME	ROLE ON PROJECT				SALARY REQUESTED	FRINGE BENEFITS	TOTAL
	Principal Investigator						
SUBTOTALS →							
CONSULTANT COSTS							
MAJOR EQUIPMENT (<i>Itemize</i>)							
MATERIALS, SUPPLIES AND CONSUMABLES (<i>Itemize by category</i>)							
TRAVEL COSTS							
RESEARCH-RELATED SUBJECT COSTS	INPATIENT						
	OUTPATIENT						
OTHER DIRECT COSTS (<i>Itemize by category</i>)							
CONSORTIUM/SUBAWARD**	DIRECT COSTS						
	INDIRECT COSTS (FACILITIES/ADMINISTRATIVE COSTS)						
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD (<i>Item 7a, Cover Page</i>)						\$	
TOTAL INDIRECT COSTS OF APPLICANT ORGANIZATION FOR INITIAL BUDGET PERIOD							
TOTAL DIRECT AND INDIRECT COSTS FOR INITIAL PERIOD (<i>Item 7b, Cover Page</i>)						\$	

***Include a separate Form of an initial 12 month budget for each consortium/subaward organization.*

Principal Investigator/Program Director (Last, First, Middle):

SUMMARY BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT

BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD (from Form D)	ADDITIONAL YEARS OF SUPPORT REQUESTED	
		2nd	3 rd (<i>clinical only</i>)
PERSONNEL: <i>Salary and fringe benefits. Applicant organization only.</i>			
CONSULTANT COSTS			
MAJOR EQUIPMENT			
MATERIALS, SUPPLIES AND CONSUMABLES			
TRAVEL COSTS			
RESEARCH-RELATED SUBJECT CARE COSTS	INPATIENT		
	OUTPATIENT		
OTHER EXPENSES			
CONSORTIUM SUBAWARD**	DIRECT COSTS		
	INDIRECT COSTS (F&A)		
SUBTOTAL DIRECT COSTS PER YEAR			
SUBTOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT (<i>Item 8a, Cover Page</i>)			\$
INDIRECT COSTS OF APPLICANT ORGANIZATION			
TOTAL DIRECT AND INDIRECT COSTS PER YEAR			
TOTAL COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT (<i>Item 8b Cover Page</i>)			\$
** Include a separate Form I for the entire proposed project period for each consortium/subaward organization.			
JUSTIFICATION. Use continuation pages as needed.			

Principal Investigator/Program Director (Last, First, Middle):

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form B. Follow this format for each person. **Do not exceed 3 pages per individual for full proposals or 2 pages for preproposals.**

NAME	POSITION TITLE		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
RESEARCH AND PROFESSIONAL EXPERIENCE			
Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.			
Selected peer-reviewed publications (in chronological order). Do not cite manuscripts that are not yet accepted or published.			
Current research. List selected ongoing or completed (during the last three years) research projects. Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, co-investigator, consultant) in the research project. Do not list award amounts or percent effort in projects.			

AVAILABLE FACILITIES AND MAJOR EQUIPMENT

Describe the facilities available for performance of the proposed request and any additional facilities or equipment proposed for acquisition at no cost to USAMRMC. Indicate if government-owned facility or equipment is proposed for use. Reference should be made to the original or present contract under which the facilities or equipment items are now accountable.

FACILITIES: For each performance site identified on Form B, describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:

Clinical:

Animal:

Computer:

Office:

Other:

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

INSTRUCTIONS FOR SUBMISSION OF PROPOSALS TO USAMRMC
FOR ADVANCED FIRST-RESPONDER
RESUSCITATION FLUIDS AND ADJUNCT THERAPIES

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III.2.2 Performance Site(s) of Proposed Research
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I. FORMS AND SUBMISSION INFORMATION

I.1 Access to Instructions and Forms

- This is a supplement to US Army Medical Research and Materiel Command – Department of Defense Broad Agency Announcement BAA 05-1

Preproposals/proposals submitted for Advanced-First Responder Resuscitation Fluids (AFRRF) awards have specific requirements that are in addition to the U.S. Army Medical Research and Materiel Command (USAMRMC) general requirements.

The forms in this proposal packet are tailored to the AFRRF Supplement to BAA 05-1. Broad Area Announcement 05-1 proposal submission instructions and forms for USAMRMC general awards are available at:

http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm, which can be used in place of the AFRRF formats, as long as the requested AFRRF information and AFRRF defined page limitations are followed. These forms are interactive and may be completed electronically for inclusion on a CD/DVD for submission.

- If you have questions concerning the preparation of preproposals or proposals, please contact: Cheryl Miles, 301-619-7148, cheryl.miles@det.amedd.army.mil

I.2 Mailing Instructions

- Follow mailing directions as indicated for other USAMRMC awards and submit the preproposal or full proposal (with appendices as a separate file, if needed) on one CD/DVD in PDF or Microsoft Office format. Label the disk with the name of the principal investigator and organization and the email address and phone number of a point-of-contact individual.

Mail, courier, or hand-deliver submissions to:

USAMRAA

ATTN: [add announcement number here, e.g., W81XWY-BAA 04-1-AFRRF]

820 Chandler Street

Fort Detrick, MD 21702-5014

II. INSTRUCTIONS FOR PREPARING THE AFRRF PROPOSAL PACKET

All pages of the completed preproposal/proposal should comply with formatting requirements.

- These instructions pertain to applications to USAMRMC for research project awards for AFRRF therapies. These instructions are meant to comply with USAMRMC proposal requirements
- Forms specific to the AFRRF proposal are available in Microsoft Office and PDF formats.
- All requested information must be submitted in English in the format required.
- Preproposals are to follow the same formatting and content requirements as full proposals, except where noted. For example, preproposals have different page limitations. (See Table 1.)

II.1 Proprietary and Confidential Information

- Offerors are discouraged from submitting information considered proprietary or confidential unless it is deemed essential for proper evaluation of the proposal. However, when the proposal contains information that constitutes trade secrets, or information that is confidential or privileged, mark the pages **CONFIDENTIAL**.

II.2 Format Specifications

- The proposal must contain only material that reproduces well when photocopied in black and white.

II.2.1 Format Pages

- **Format pages** (forms) are available for eleven (11) major sections of the proposal packet as indicated in Table 1. Other required forms are available from USAMRMC (http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm). These forms are intended to assist in the development of specific sections of the proposal. Alternatively, you may create a page similar to any format provided as long as all the requisite information is included and format requirements are met.

II.2.2 Font

- Adherence to font and margin requirements is mandatory.
- Suggested typeface: Arial, Helvetica, Palatino Linotype or Georgia.

- **Use a font size of 12 points.** You may use a smaller font size for figures, figure legends, graphs, diagrams, charts, tables, and footnotes but it must be in black font, and readily legible.
- Type density of line must be no more than 15 (total) characters per horizontal inch, including the spaces between words and punctuation.
- The proposal must be single-spaced having a line density per page of no more than five (5) lines per vertical inch.
- Use black font that can be clearly copied.
- Print must be clear and legible.

II.2.3 Page Size, Margins, Pagination, and Running Header

- Use **standard 8 1/2" x 11"** page size.
- Use at least one-half inch margins for top, bottom, and right and one inch left margins for all pages, including continuation pages and the Appendix. Print area should be no more than 7.0 x 10.0 inches (approximately 18 cm x 25.5 cm).
- The proposal must be single-sided (exception: Appendix may be double sided).
- All pages must be numbered (exception: Appendix may be unnumbered). Center numbers at the bottom of the page; **make sure numbers do not enter into the one-half inch bottom margin.**
- Follow Table of Contents format (Form C) to order pages in the proposal, which is the same as the organization of major sections in Table 1. Beginning with the Proposal Cover Page, consecutively number pages throughout the proposal including continuation pages. Do not use suffixes (e.g., do not use 5a, 5b). List the assigned page numbers for all major headings of the proposal packet in the Table of Contents (Form C).
- Beginning with page two (2) of the proposal, specify the **name of the Principal Investigator or Program Director at the top of every page as a running header, including continuation pages and Appendix pages, making sure that names do not enter into the one-half inch top margin.**

II.2.4 Abbreviations, Acronyms, and Symbols

- Unless the abbreviation, acronym, or symbol is universally known, spell out the term and note its abbreviation in parentheses the first time the term is used. All abbreviations used in the Abstract, Product/Agent, Military Relevance, and Research Plan sections of the proposal must be defined the first time they are used in each of these sections.
- List abbreviations, acronyms, and symbols on one page following the Research Bibliography.

II.2.5 Page Limitations

- All proposals must be self-contained within specified page limitations given in Table 1. Hence, content displayed at Internet website addresses (URLs) may not be used to provide information necessary to the review. Note that reference to such a website could compromise the offeror's anonymity.
- **Proposals that exceed the page limitations will be returned without review.**

Table 1. Forms, Page Limitations, and Related Specifications

Section	Form	Page Limit, Proposal (Preproposal)	Related Specifications
Proposal Cover Page	A	1	Do not exceed 120 characters in the title of research project, including the spaces between words and punctuation
Abstract, Performance Sites, Key Personnel, Other Significant Contributors	B	None	Abstract must not exceed space provided on Form B
Table of Contents	C	None	

Statement of Work	D	1	
Product/Agent	E	2 (1)	
Military Relevance of Product/Agent	F	1	
Research Plan	G	Total = 8 (4)	Page limits are for all text, figures, charts, tables, and diagrams included in the Research Plan.
Specific Aims, Background, and Significance sub-section limit:		2 (1)	
Preliminary Data sub-section limit:		2 (1)	
Research Design and Methods sub-section limit:		4 (2)	
Research Bibliography	None	None	Each continuation page must bear the heading: <u>Research Bibliography</u>
Acronym, Symbol Definition	None	None	
Detailed Cost Estimate for Initial 12 Month Budget Period	H	None	
Summary Budget for Entire Proposed Period of Support	I	None	
Budgets Pertaining to Consortium/Subawards	H/I	None	
Biographical Sketches of Key Personnel and Other Significant Contributors	J	3 (2) per individual	
Existing/Pending Support and Past Related Efforts	None	None	
Consortium/Contractual Arrangements for Proposed Research	None	None	
Letters Confirming Collaboration	None	None	(Full proposals only)
Available Facilities and Major Equipment	K	None	
Institution Safety Program Plan	Available	None	(Full proposals only) See Appendix 11 of the USAMRMC general proposal instructions and forms.*
Certificate of Environmental Compliance	Available	None	(Full proposals only) Submit one certificate for each site conducting research under the proposal, including subcontractors. See Appendix 8 of USAMRMC general proposal instructions and forms.*
Human Use Required Information and Approval	Available	None	(Full proposals only) See Appendix 9 of the USAMRMC general proposal instructions and forms. Must be submitted within 60 days of award if proposal is approved for funding.*

Animal Use Required Information and Approval	Available	None	(Full proposals only) See Appendix 10 of the USAMRMC general proposal instructions and forms. Must be submitted within 60 days of award if proposal is approved for funding.*
Appendix	None	None	(Full proposals only) Appendix material might not be reviewed. Hence, do not include in the Appendix experimental data or other information critical to the review. Do not use the Appendix to circumvent the page requirements of the body of the proposal. Indicate conclusion of Appendix material with a line stating "END OF APPENDIX MATERIAL"

*http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm

III. INSTRUCTIONS FOR SPECIFIC ITEMS

Follow instructions on proposal forms. Additional instructions are provided below to assist in form completion.

III.1 Proposal Cover Page (Form A)

- The entire Proposal Cover Page (page 1 Form A) must be printed on a single page. The Proposal Cover Page must not have any shading or colors.
- Indicate whether this is a preproposal or full proposal.
- Choose a descriptive title that is specifically appropriate.
- If this proposal is in response to a specific request or Broad Agency Announcement (BAA), insert the appropriate announcement number and title of that announcement.
- If this proposal follows the previous submission of a preproposal of the same project, provide the title of the preproposal and the USAMRMC assigned log number.

III.1.1 Cover Page Item 3: Principal Investigator/Program Director

- The name of the Principal Investigator/ Program Director should be the one person responsible to the applicant organization for the scientific and technical direction of the project.
- Indicate up to three academic and professional degrees or other credentials, such as licenses (e.g., R.N.).
- Provide the academic or professional title of the Principal Investigator/Program Director. If there is more than one position title, indicate the one most relevant to the proposed project (e.g., Chief of Surgical Service).
- Indicate the school, college, or other major subdivision, such as medical, engineering, graduate, or nursing. If there is no such subdivision, enter "None."

III.1.2 Cover Page Item 4: Human Subjects Research

Research that involves obtaining private information or identifiable human biological specimens (such as blood and tissue samples) is considered human subjects research (45 CFR Part 46).

- Answer "Yes" if research activities involving human subjects are planned at any time during the proposed project period, even if the research is exempt from regulations for the protection of human subjects. Note: use of cadaver specimens are not human subjects research.
- If the study might involve human subjects during the proposed project period, but does not have definite plans at the time of application, the Principal Investigator will need to provide the Research Plan before the research can occur.
- Enter the institution's current Multiple Project Assurance (MPA) or Federal Wide Assurance (FWA) number with the U.S. Department of Health and Human Services Office for Human Research Protections in item 4a. See section III.18 on Human Use Required Information and Approval. See supplemental instructions in Appendix 9 of the general USAMRMC proposal instructions particularly part 12, Assurances, and part 3-c, Multi-site Protocol Review, at http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm

III.1.3 Cover Page Item 5: Use of Vertebrate Animals

- Enter the Institutional Animal Care and Use Committee (IACUC) approval date in item 5b if such approval has been obtained. IACUC protocol review and approval may follow proposal submission for peer review but must be provided prior to Department of Defense approval of the proposed animal research. See section III.19 on Animal Use Required Information and Approval. See supplemental instructions in Appendix 10 of the general USAMRMC proposal instructions particularly part 13 on IACUC approval at http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm

III.1.4 Cover Page Item 6, Item 7, and Item 8: Dates and Budget of Proposed Period of Support

- For duration (in years), allow time to complete research efforts and complete final report. Request no more than 2 years of support for non-clinical studies and no more than 3 years of support for human clinical studies. Note: Some mechanisms specify fewer years.
- Proposal valid until date: allow a minimum of six months from the date of submission.
- Dollar amounts must be in U.S. dollars.
- Initial budget period refers to the first 12 month funding period. These direct and total costs are derived from Form H.
- The direct and total costs of the proposed period of support are derived from Form I.

III.1.5 Cover Page Item 9 to Item 12: Applicant Organization and Authorized Representative

- Awards are made to organizations, not individuals. Any organization receiving an award under the BAA must be registered in the Central Contractor Registration database, which requires a Data Universal Numbering System (DUNS) number. Registration may be accomplished online via the internet at <http://www.ccr.gov/>
- For entity identification of the organization, enter the DUNS number. The DUNS is a nine-digit Universal Identifier number assigned by Dun and Bradstreet Information Services. If the organization does not have a DUNS number, an authorized organizational official should complete the electronic US D&B D-U-N-S Number Request Form or call 1-866-705-5711 (toll-free) to obtain an organizational number immediately at no charge. Principal investigators do not need to register for an individual DUNS number.
- Name the authorized representative of the one organization that will be legally and financially responsible for the conduct of activities supported by the award (Item 10).
- Enter the name and contact information for an alternate Principal Investigator (Item 11) and alternate organizational representative (Item 12).

III.1.6 Cover Page Item 13 and Item 14: Official Signatures

- Electronic signatures are acceptable or the signed forms can be scanned and included in the proposal.
- "Per" signatures (signing as the designated official or without the formal delegation) are not acceptable. The date of signature must be included.
- "For" signatures are acceptable for Item 14 only (i.e., if the official designated to sign for the applicant organization is not available to sign) only another institutional official with formal delegated authority to act in his/her behalf may sign as "acting for" such official. ***In signing the Proposal Cover Page, the duly authorized representative of the applicant organization certifies that the applicant organization will comply with all applicable policies, assurances and/or certifications referenced in the proposal.*** The applicant organization is responsible for verifying its eligibility and the accuracy, validity, and conformity with the most current institutional guidelines of all the administrative, fiscal, and scientific information in the proposal, including the Facilities and Administrative rate. Deliberate withholding, falsification, or misrepresentation of information could result in administrative actions, such as withdrawal of a proposal, suspension and/or termination of an award, debarment of individuals, as well as possible criminal penalties. The signer further certifies that the applicant organization will be accountable both for the appropriate use of any funds awarded and for the performance of the grant-supported project or activities resulting from this proposal. The grantee institution may be liable for the reimbursement of funds associated with any inappropriate or fraudulent conduct of the project activity.

III.2 Abstract, Performance Sites, Key Personnel, Other Significant Contributors (Form B)

Do NOT insert additional pages between Proposal Cover Page 1 (Form A) and Page 2 (Form B). Information for the non-abstract sections of Form B can be continued on consecutively numbered pages.

III.2.1 Abstract: Project Summary and Relevance

- Do not exceed the defined space provided for the abstract on Form B. This space is 6.25 inches horizontal by 6.5 inches vertical.
- The abstract serves as a succinct and accurate description of the proposed work when separated from the proposal. As instructed on Form B, be sure to identify the product/agent to be tested and the relevance of the project to the treatment of hemorrhagic shock and to combat casualty care. State what is unique and innovative about your approach. Avoid describing past accomplishments and the use of the first person.
- Spell out all Greek or other non-English letters.
- Do not include figures or tables in the abstract.
- Do not include proprietary, confidential information or trade secrets in the abstract or information subject to restrictions on distribution for evaluation purposes.
- A sample technical abstract is available at http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm.

III.2.2 Performance Site(s) of Proposed Research

- If there is more than one performance site where the work described in the Research Plan (Form G) will be conducted, list all the sites, including the Department of Veterans Affairs (V.A.) facilities and foreign sites, and provide an explanation in the Available Facilities and Major Equipment (Form K) section of the proposal. One of the sites indicated must be the applicant organization. Additional information about the performance sites is also detailed in section III.15 on Available Facilities and Major Equipment.

III.2.3 Key Personnel

- In addition to the Principal Investigator, Key Personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries are requested. Typically, these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level should be included if their involvement meets the definition of Key Personnel. **Consultants should also be included if they meet the same definition.**
- "Zero percent" effort or "as needed" are not acceptable levels of involvement for those designated as Key Personnel.
- Key Personnel are expected to work collaboratively and collectively maintain sharp focus toward achieving project objectives.
- Letters of support from Key Personnel are to be included as described in Letters Confirming Collaboration.

III.2.4 Other Significant Contributors

- This category identifies individuals who have committed to contribute to the scientific development or execution of the project, but are not committing any specified measurable effort to the project. These individuals are typically presented at "zero percent" effort or "as needed." Do not list individuals with measurable effort as Other Significant Contributors. Examples of Other Significant Contributors include consultants and mentors on Career awards.
- Should the level of involvement change for an individual listed in this category, they should be redesignated as Key Personnel before any compensation is charged to the project.

III.3 Table of Contents (Form C)

- The research proposal should be organized by placing major sections in the order listed in Table 1 and Form C. List the page number for each major heading in the Table of Contents. (For pagination see section II.2.3.)

III.4 Statement of Work (Form D)

- Do not exceed one page.
- The instructions on Form D for the Statement of Work (SOW) are consistent with the USAMRMC proposal preparation instructions. The SOW outlines performance expectations for the project within the timeframe of the budget period.
- A sample statement of work is available at http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm. This sample is presented in Figure 1.

SAMPLE

Statement of Work

Development of Peptide Inhibitors of the "Cancer" Receptor (CR)

Task 1. To identify the minimal region of the CR polypeptide able to inhibit intact CR when co-expressed in cultured cells (Months 1-18):

- Develop a series of plasmids for expressing the CR open reading frame (Months 1-7).
- Perform assays to ascertain which fragments of CR block DNA-binding (Months 7-18).
- Confirm that fragments of the CR open reading frame that block DNA-binding activity also inhibit CR function *in vivo* (Months 18-24).

Task 2. To identify short peptides modeled after the receptor that act as inhibitors of DNA-binding and subunit association (Months 18-26):

- Obtain synthetic CR peptides (Months 18-21).
- Test the effect of synthetic peptides on the DNA-binding activity of CR (Months 20-24).
- Characterize the inhibitory potency of active peptides and attempt to optimize the effect by testing additional overlapping peptides (Months 21-36).
- Perform feasibility experiments to assess the ability of selected peptides to inhibit CR function in cultured cells (Months 20-36).

Figure 1. An example Statement of Work presented by the U.S. Army Medical Research and Materiel Command (<http://www.usamraa.army.mil/pages/index.cfm>).

III.5 Product/Agent (Form E)

- Do not exceed 2 pages for full proposals or 1 page for preproposals.
- The references cited on Form E *should be limited to relevant and current literature*. These references should be listed in the Research Bibliography.

III.5.1 Product/Agent: Drug Information

- Provide characteristics of the product/agent that are useful for assessing its safety and efficacy in treating battlefield hemorrhage. Note any known drug interactions, counterindications, known adverse events, and biohazard risk from expired, crushed/damaged, or leftover product. Current and target product forms should be described.

III.5.2 Product/Agent: Timeline of Product Development

- Outline a timeline of product development for approval in the US market for a trauma indication. Note if there are ongoing or planned clinical trials for any indications. Do not confuse this timeline of product development with the tentative timetable for the proposed project in the Research Plan.
- Identify the product/agent's current status in the US Food and Drug Administration's approval process with respect to both a trauma-hemorrhage indication and any other indications. Please include approved route(s) of administration. If product/agent is not approved for use in the United States but is in the European market, note this.
- Succinctly state how the proposed project will further the product/agent's development.

III.5.3 Product/Agent: Manufacturer

- If the product manufacturer is a partner in the project, contributing to the scientific development or execution of the project in a substantive, measurable way, their representative should be listed with Key Personnel or Other Significant Contributors on Form B.
- If the product manufacturer is donating product for use in the project, this should be indicated in the budget (Form H) under supplies or patient care costs.

III.5.4 Product/Agent: Intellectual Property Protection

- Please identify intellectual property ownership, including expiration dates of patents and licenses.

III.5.5 Product/Agent: Outline Process for Commercial Development

- Provide information that supports the commercial appeal and viability of the proposed product/agent in the non-military environment. If there is a commercial development plan, provide a brief outline of this process.

III.6 Military Relevance of Product/Agent (Form F)

- Do not exceed 1 page.
- Using and supplementing product/agent information from Form E, compare the proposed product/agent to the military product "requirements" or performance goals specified in the supplement to the request for proposal to which you are responding. For example, discuss product storage and transport requirements, shelf-life/stability under extreme environmental conditions, weight and cube per unit dose, and functionality in the combat environment.

III.7 Research Plan (Form G)

Do not exceed eight (8) pages for full proposals or four (4) pages for preproposals. All tables, graphs, figures, diagrams, and charts must be included within the page limit. Proposals that exceed the page limits will be returned without review.

- The format for preparing this section is provided on Form G. The research plan is a detailed description of the research to be undertaken and is analogous to the "Body of Proposal" in the general USAMRMC proposal format.
- Glossy photographs of material such as electron micrographs or gels should be scanned to include them within the page limitations of the Research Plan.
- Offerors are discouraged from submitting information considered proprietary unless it is deemed essential for proper evaluation of the proposal. However, when the proposal contains information that constitutes trade secrets, or information that is confidential or privileged, mark the pages "**CONFIDENTIAL**".
- The references cited in the Research Plan should be limited to relevant and current literature. These references should be listed in the Research Bibliography.

III.7.1 Research Plan: Specific Aims, Background and Significance

- Do not exceed 2 pages for full proposals or 1 page for preproposals.
- State the goal of the specific research proposed and hypothesis to be tested.
- Briefly sketch the background leading to the present proposal, critically evaluate existing knowledge, and specifically identify the gaps that the project is intended to fill.
- What is the proposed mechanism of action of the experimental product/agent for use in resuscitation therapy?
- If the aims of the proposal are achieved, state how scientific knowledge or clinical practice will be advanced. Describe the relevance of the project to the treatment of hemorrhagic shock under combat conditions.
- How is this approach to treating trauma/hemorrhage in a combat environment unique and innovative? Describe the effect of these studies on the concepts, methods, technologies, treatments, or services that drive this field.

III.7.2 Research Plan: Preliminary Data

- Do not exceed 2 pages for full proposals or 1 page for preproposals.
- Provide an account of the Principal Investigator/Program Director's preliminary studies and preliminary data pertinent to this proposal. Demonstrate that the product can be administered under circumstances proposed.

III.7.3 Research Plan: Design and Methods

- Do not exceed 4 pages for full proposals or 2 pages for preproposals.
- Particular attention will be paid to proposed experiments that might indicate functionality in a combat-injury environment.
- Describe the research design, procedures, and analyses to be used to accomplish the specific aims of the project in sufficient detail for evaluation. Include how the data will be collected, analyzed, and interpreted as well as the data-sharing plan as appropriate.
- Specify the type and number of subjects to be studied and for clinical studies, specify the power analysis. Define the end points and the statistical protocols and analysis.
- Describe any novel concepts, approaches, tools, or technologies for the proposed studies and its advantage over existing methodologies.
- Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. Factors that impact the evaluation of the proposal quality include whether the limitations and uncertainties of the experiment are addressed and whether there is bias, critical omissions, oversights, and/or inconsistencies.
- Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised.

As part of this section, provide a tentative timetable for the proposed project. Do not confuse this project timetable with the timeline of product development in the Product/Agent section of the proposal.

III.7.3.1 Research Plan: Protection of Human Subjects

- For all research involving human subjects, a part of the peer review process will include careful consideration of the protections from research risks, as well as the appropriate inclusion of women and minorities, based on the information in the proposal.
- If you plan to enroll subjects without individual informed consent (*i.e.*, enrollment during the pre-hospital phase of emergent care) discuss any obstacles that might impede the experimental treatment from realistically securing “community consent” (*i.e.*, approval by representatives of the community charged with evaluating product safety data).
- If you are planning a clinical trial, provide a general description of your Data and Safety Monitoring Plan that will be used to provide oversight and monitoring of the safety of participants and the validity and integrity of the data.
- Should the proposal be accepted for funding, human use information will be required within 60 days of the award. See section III.18 on Human Use Required Information and Approval.

III.7.3.2 Research Plan: Use of Vertebrate Animals

- If the use of vertebrate animals is planned, discuss how the animal model is relevant to the military condition (*e.g.*, hemorrhagic shock under combat conditions).
- Studies in the late preclinical stage of product development are encouraged to include:
 - Two species of large animals
 - Uncontrolled hemorrhage to reflect battlefield conditions (*i.e.*, short-term) until evacuation (*e.g.*, 6 to 12 hours) long-term, without clamp, without anesthesia as a variable
 - Assess end organ damage
 - Measure increased survival as an end point
- See section III.19 on Animal Use Required Information and Approval for further instructions. Required materials must be submitted within 60 days of award if proposal is approved for funding.

III.8 Research Bibliography

- Conform to formatting requirements of the proposal packet (*e.g.*, page margins, page numbering). **Each continuation page in this section must bear the heading of Research Bibliography** to easily distinguish it from the peer-reviewed publication sections of the biographical sketches of Key Personnel/Significant Contributors.
- The reference citations should be limited to relevant and current literature. Include references cited in sections Product/Agent (Form E) and Military Relevance of Product/Agent (Form F) and Research Plan (Form G) of the proposal packet. While there is not a page limitation, it is important to be concise and to select only those literature references pertinent to the proposed research.
- Each reference citation must include the title, names of all authors, book or journal, volume number, page numbers, and year of publication.
- Do not send or attach copies of articles.

III.9 Acronym/Symbol Definition

- Provide a glossary of acronyms and symbols that might not be familiar to reviewers who are not current in the proposal’s research area.

III.10 Budget Instructions (Form H and Form I)

- All proposals should submit Form H: Detailed Cost Estimate for Initial 12 Month Budget Period, **and** Form I: Summary Budget for Entire Proposed Period of Support.
- **Follow instructions for Detailed Cost Estimate in section F of the USAMRMC proposal preparation instructions** [**http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm**](http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm) **for information to complete the budget and conform to regulations and principles that apply to commercial firms, educational institutions, nonprofit organizations, and state, local, and tribal governments.**

- Each item listed on Form H must be clearly justified on Form I, including items categorized as Other Expenses. For offerors performing outside of the United States, justify conversion rates used to convert local currency into U.S. dollars.
- Values in the "Total" column of the initial budget period on Form H are carried over and entered into the respective column on Form I.
- Enter the total annual costs for additional years of support on Form I. Request no more than 2 total years of support for non-clinical studies and no more than 3 total years of support for human clinical studies.

III.10.1 Budget: Additional Instructions for Patient Care Costs

- If inpatient and/or outpatient costs are requested, provide the names of any hospitals and/or clinics and the amounts requested for each on Form I under Justification.
- Indicate, in detail, the basis for estimating costs in this category, including the number of patient days, estimated cost per day, and cost per test or treatment. If both inpatient and outpatient costs are requested, provide information for each separately. If multiple sites are to be used, provide detailed information by site.
- Include information regarding projected patient accrual for the project/budget periods and relate this information to the budget request for patient care costs. If patient accrual is anticipated to be lower at the start or during the course of the project, plan budget(s) accordingly.
- Provide specific information regarding anticipated sources of other support for patient care costs (e.g., third party recovery or pharmaceutical companies).

III.10.2 Budget: Additional Instructions for Consortium/Contractual Costs

- The applicant organization should note the sum of direct costs of all consortium/contractual participants and the sum of F&A costs of all consortium/contractual participants on Form H and Form I. When F&A costs are requested by a consortium organization, provide the F&A cost base and rate in the Justification section of Form I.
- In the proposal, include a separate detailed budget (Form H) for each participating consortium/contractual organization. For each, label that page accordingly with name of the organization at the top of the page. If consortium activity exceeds one year, also include Form I for that organization.

III.11 Biographical Sketch (Form J)

- Include Biographical Sketches of all Key Personnel and Other Significant Contributors, including consultants, following the order as listed on Form B. The Biographical Sketch may not exceed 3 pages per individual for full proposals and 2 pages for preproposals.
- Use the heading Selected Peer-Reviewed Publications by Key Personnel/Significant Contributors for the list of selected peer-reviewed publications and also insert this heading at the top of the continuation page if the section is continued. Such a heading easily distinguishes this list from the Research Bibliography section of the proposal packet.
- **Current Research** should highlight your recent scientific accomplishments. This information is used by the reviewers to assess each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team.

III.12 Existing/Pending Support and Past Related Efforts

- For the Principal Investigator and Key Personnel, list the title, time commitments, supporting agency and level of funding for all existing and pending research projects. Provide justification for USAMRMC support where the projects overlap or parallel.
- Prepare a synopsis of grants on similar or related effort for the past 3 years, including:
 - Specifics on each grant, including types and dates of performance
 - The name and address of the Procuring Contracting/Grant Officer
 - The negotiated price, and the final cost to the Government, with reasons for any variance

III.13 Consortium/Contractual Arrangements for Proposed Research

- Explain the programmatic, fiscal, and administrative arrangements to be made between the applicant organization and the consortium organization(s). If consortium/ contractual activities represent a significant portion of the overall project, explain why the applicant organization, rather than the ultimate performer of the activities, should be the grantee.

III.14 Letters Confirming Collaboration

- (Full proposals only) Include letters of support from Key Personnel.
- Include letters from all consultants that confirm their roles in the project and their rate/charge for consulting services.
- Include a letter of support from the product manufacturer, if indicated on Form E.
- **Follow instructions for Collaboration and Joint Sponsorship in part G, item 5 of the USAMRMC proposal preparation instructions http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm**

III.15 Available Facilities and Major Equipment (Form K)

- In describing the scientific environment in which the work will be done, discuss ways in which the proposed studies will benefit from unique features of the scientific environment, or subject populations, or the employment of useful collaborative arrangements.

- If proposals include use of Government facilities, offerors will be expected to conclude arrangements for commercial services with the providing Government facility.
- Additional facility information and assurance statements are required for full proposals. See Institution Safety Program Plan.

III.16 Institution Safety Program Plan

- (Full proposals only) Institution-based safety program plan information and assurance statements are required. Follow instructions for Safety Program Plan in Appendix 11 of the USAMRMC proposal preparation instructions at http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm to include the required components.

III.17 Certificate of Environmental Compliance

- (Full proposals only) Information regarding environmental compliance must be provided. Follow instructions for Certificate of Environmental Compliance in Appendix 8 of the USAMRMC proposal preparation instructions at http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm to include the required components.

III.18 Human Use Required Information and Approval

USAMRMC does not require Institutional Review Board (IRB) approval and certification of the proposed research prior to peer-review of a proposal. Required materials must be submitted within 60 days of award if proposal is approved for funding.

- (Full proposals only) See Appendix 9 of the USAMRMC proposal preparation instructions at http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm to include the required components.
- Any modification of the Research Plan section of the proposal required by the IRB or to address human subjects concerns raised during review must be submitted for approval before award.
- If a research proposal involving human subjects, human anatomical subjects, or privileged or protected health information is recommended for funding, a research protocol must be submitted to the Human Subjects Research Review Board (HSRRB) for review and approval. **HSRRB approval must be obtained prior to initiation of Department of Defense sponsored research.**

III.19 Animal Use Required Information and Approval

USAMRMC does not require IACUC approval of the proposed research before peer review of a proposal. Required materials must be submitted within 60 days of award if proposal is approved for funding.

- (Full proposals only) See Appendix 10 of the USAMRMC proposal preparation instructions at http://www.usamraa.army.mil/pages/baa_paa/baa_05_1.cfm to include the required components.
- The principal investigator/program director must submit any modification of the Research Plan section of the proposal required by the IACUC with the follow-up verification.
- Research that generates preclinical safety data intended to support a research or marketing permit for products regulated by the U.S. Food and Drug Administration will be in conformance with Good Laboratory Practices.

III.20 Appendix

- (Full proposals only) The proposal and Appendix should be separate documents. **Include one file of all Appendix material, as a separate document from the body of the proposal, on the same CD/DVD as the proposal.**
- The Appendix will be sent only to primary reviewers and might not be reviewed.
- In the Appendix, identify each item with the name of the principal investigator. Appendix material may be single-sided or double-sided and does not require page numbers. Indicate conclusion of Appendix material with a line stating "END OF APPENDIX MATERIAL" after completion of Appendix and within one-half inch margin requirement.
- The following materials may be scanned and included in the Appendix:
 - Surveys, questionnaires, data collection instruments, clinical protocols, and informed consent documents.
- Glossy photographs or color images of gels, micrographs, etc., critical to the proposal review should be electronically scanned so they can be included within the page limits of the relevant section of the body of the proposal rather than in the Appendix.

Do not use the Appendix to circumvent the page limitations of the body of the proposal. Graphs, diagrams, tables, and charts critical to the proposal review should be included in the body of the proposal and must not be included in the Appendix. A proposal that does not observe these limitations will be returned.

APPENDIX C: REPORT

Reference:

Life Sciences Research Office (2005) Recommendations for Reviewing Research on Advanced First-Responder Resuscitation Fluids and Adjunct Therapies. (Klein, C. J., ed.). Bethesda, MD: Life Sciences Research Office, Inc.

**RECOMMENDATIONS FOR REVIEWING RESEARCH ON
ADVANCED FIRST-RESPONDER RESUSCITATION FLUIDS
AND ADJUNCT THERAPIES**

July 2005

Editor:
Catherine J. Klein, Ph.D., R.D., C.N.S.D.

Sponsor:
The United States Army Medical Research and Materiel Command
and
The Office of Naval Research



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PREFACE

The Life Sciences Research Office, Inc. (LSRO) provides scientific assessments of topics in the biomedical sciences. LSRO reports are based on comprehensive literature reviews and the scientific opinions of knowledgeable investigators who work in relevant areas of biology and medicine.

This LSRO study, Recommendations for Reviewing Research on Advanced First-Responder Resuscitation Fluids and Adjunct Therapies, was initiated by the U.S. Army Medical Research and Materiel Command (USAMRMC) (Ft. Detrick, MD) in cooperation with the Office of Naval Research (Arlington, VA), in accordance with a contract between LSRO and the USAMRMC. This report was supported and governed in accordance with Contract No. W81XWH-04-C-0569, as amended on November 18, 2004, (P00001), between the United States Army Medical Research Acquisition Activity and LSRO.

This report was based on discussions of, and materials evaluated by, an *ad hoc* expert panel convened by LSRO. LSRO independently appointed members of the expert panel according to their qualifications, experience, and judgment, with due considerations for balance and breadth in the appropriate professional disciplines. Members of the expert panel and others who assisted in the preparation of the report are identified in the report. The expert panel convened three times (two 2-day meetings and one conference call) to assess the available data and make recommendations.

The study described in this report was a two-phase project. During Phase I, 59 preproposals for advanced first-responder resuscitation fluid (AFRRF) were reviewed, evaluated and ranked for military relevance and scientific merit. Phase II yielded recommendations for the future evaluation of AFRRF proposals.

This detailed LSRO report reviews AFRRF preproposals and highlights positive characteristics of the review process. It is intended to be used by the sponsor, grant applicants, and future expert peer-reviewers. The expert panel directed the review of data and the ranking of preproposals. The expert panel also heard from outside speakers and from military experts, who summarized considerations for development of AFRRF products for use in combat. LSRO staff and members of the expert panel considered all available information when drafting the report, considered reviewers' comments, and provided additional documentation and viewpoints for incorporation into the final report.

LSRO was contractually obligated to provide the sponsor with an opportunity to review the methods used by the expert panel to score and rank the preproposals. After the sponsor reviewed these methods, the findings of the expert panel were released to the sponsor. The sponsor, not LSRO, will decide which preproposals will be accepted for the purpose of invitation-only submission of a full formal proposal for competitive funding in the next AFRRF funding cycle.

Provisions were made to review but not reveal confidential and proprietary information by executing confidentiality agreements. The following confidential LSRO findings and data tables will be provided to the sponsor in a supplement to this report:

- A list of all preproposals meeting the inclusion criteria
- Individual critiques for each preproposal considered by the expert panel, with brief summaries of the preproposal's strengths and limitations
- A table of all preproposal scores and rankings
- A table categorizing the mode of action, stage of product development, and potential commercial viability for proposed products
- Digital copy of suggested proposal instructions and forms
- A list of LSRO contacts made in association with this AFRRF report

The final report was reviewed and approved by the expert panel and the LSRO Board of Directors. On completion of these review procedures, the Executive Director of LSRO approved and transmitted the report to the USAMRMC.

LSRO is solely responsible for the content of this report. This report was developed independently, and the conclusions drawn herein do not necessarily reflect the views or policies of the USAMRMC or of any of its employees. Although LSRO accepts full responsibility for the study conclusions and accuracy of the report, the report does not necessarily represent the opinion of the LSRO Board of Directors. The mention of trade names, commercial products, or organizations does not imply endorsement by LSRO.

*Michael Falk, PhD.
Executive Director,
Life Sciences Research Office, Inc.
June 30, 2005*

ACKNOWLEDGEMENT

The Life Sciences Research Office, Inc. appreciates the outstanding contribution of James L. Atkins, M.D., Ph.D. in organizing presentations on behalf of the sponsors, the U.S. Army Medical Research and Materiel Command and the Office of Naval Research, to educate the Advanced First-Responder Resuscitation Fluid expert panel on factors contributing to the military relevance of products for combat use.

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EXECUTIVE SUMMARY

The U.S. Army Medical Research and Materiel Command (USAMRMC) and the Office of Naval Research (ONR) are seeking novel treatments to resuscitate wounded combatants. Depending on terrain, weather, and military situation, U.S. soldiers and marines wounded in combat may have to endure a prolonged period of time before evacuation to surgical care. On the battlefield, combatants who are bleeding sufficiently to compromise perfusion of vital organs require immediate medical care by a medic or combat lifesaver. Resuscitation fluid to replace lost blood volume is carried in limited supply. Products are needed that are practical to transport and use on the battlefield and which are effective in increasing survival and decreasing adverse complications during and after prolonged evacuation.

The mission of the military medical services is to conserve and maintain the fighting power of the command by attending to wounded combatants so they can return to duty. This report may further help the military to learn more about potentially useful resuscitation products under development and help investigators learn more about the military conditions in which products might be used.

BACKGROUND

In warfare, bullets and penetrating fragments from exploding munitions frequently cause life-threatening hemorrhage. Exsanguinating hemorrhage was the mechanism of death for up to 50% of wounded soldiers who perished in past conflicts, and is considered to be the major cause of death in potentially salvageable battlefield casualties. Hemorrhage from wounded limbs alone has accounted for nearly one-tenth of all combat deaths, a portion of which were considered preventable had appropriate pre-hospital care been provided. To help address this issue, the military has improved the design and supply of tourniquets. Once bleeding is under control, and in the case of uncontrolled torso bleeding, life is sustained on the battlefield and in transit to surgical care units through the use of resuscitation fluids.

Prior to testing a new treatment in humans, medical products must undergo animal testing to address questions of safety and effectiveness. Developing new resuscitation fluid products is a considerable undertaking, requiring the commitment of considerable time and resources to secure approval by the U.S. Food and Drug Administration (FDA). Therefore, products that are relatively far along in development, that have preliminary data establishing safety and effectiveness for resuscitation, and have the potential to meet logistical considerations imposed by combat conditions would be of greatest interest to the military.

The amount of medical product used by the military fluctuates depending on whether the military is engaged in sustained combat. Therefore, it is advantageous for the military to develop resuscitation fluid products that have dual use in both the military and civilian markets so that product production can be increased as needed.

THE STUDY

The potentially preventable loss of life from exsanguinating hemorrhage has spurred the military to consider new, low-volume resuscitation therapies to try and reduce the rate of casualties killed-in-action. Collaborating in this effort are the ONR and the USAMRMC, which together retained the Life Sciences Research Office, Inc. (LSRO) to provide an independent review, and are hereafter referred to as the sponsor. LSRO was asked to survey the types of novel resuscitation fluids and adjunct therapies under development and identify those candidates that may be worth an investment of military funding to advance research and product development.

LSRO conducted this study in two phases in conjunction with an independent, multidisciplinary expert panel of scientists:

- Phase I reviewed 59 preproposals for advanced first-responder resuscitation fluid (AFRRF) and evaluated their military relevance and scientific merit to identify and rank leading experimental therapies that were worthy of further review of a detailed full research proposal.
- Phase II examined processes and forms currently in use by the military and other federal programs for the review of scientific research. This was completed with an eye towards making recommendations for an effective program to further evaluate and prioritize current and future resuscitation technologies. The ultimate goal is to improve the quality of future proposals for the likelihood that such studies will advance development of resuscitation products for military use.

FINDINGS

Numerous products currently under development have the potential for use in civilian resuscitative care and several of these may meet the extraordinary demands for use under austere combat conditions to treat exsanguinating hemorrhage. LSRO identified 48 unique experimental products among the 59 preproposals under consideration. These products included coagulation effectors, products targeting cardiovascular responses and/or enhancing oxygen delivery, cytoprotectors supporting cell structure and metabolism, products purported to minimize inflammation and/or favorably modulate immune response, and products for blood volume expansion. LSRO prepared a critique of each preproposal for the sponsor using brief summaries prepared by two lead reviewers supplemented with comments of the expert panel.

Of the ten clinical preproposals submitted, the expert panel identified two leading candidates. Of the 49 preclinical preproposals submitted, the expert panel identified a group of five top-tier preproposals and a group of nine second-tier preproposals. The preclinical candidate with the top total score also ranked first in both military relevance and scientific merit. The five top preclinical preproposals had better scores for both military relevance and scientific merit than the two leading clinical preproposals.

Preproposals of anti-inflammatory treatments rated highly. One of the top two clinical proposals and seven of the top ten preclinical proposals included anti-inflammatory therapies.

To facilitate the future submission process for full proposals for resuscitation fluids and adjunct therapies, LSRO and the expert panel tailored proposal instructions and forms to comply with current USAMRMC requirements. Such materials and accompanying recommendations are intended to assist the sponsor in obtaining information and data useful for scientific peer review, evaluation of military relevance and assessment of commercial viability. For example, the expert panel created a standardized format for the inclusion in future proposals of detailed information characterizing the proposed experimental product, which will assist reviewers in assessing military relevance and commercial viability.

CONCLUSIONS AND PRINCIPAL RECOMMENDATIONS

LSRO and the expert panel completed all tasks requested by the sponsor. A listing of principal recommendations is summarized in Table V-1 of this report.

The expert panel recognized that one or more pharmacologic agents may be needed in addition to a blood volume expander to improve survival rates of wounded combatants. The expert panel therefore recommended that the sponsor distinguish between two product categories, encouraging investigation of novel fluids for blood volume expansion as well as emphasizing the need for pharmacologic agents that can be used with or without various resuscitation fluids.

The expert panel acknowledged the value of using conscious animals in resuscitation research to avoid artifacts resulting from anesthesia, which can obscure hemodynamic responses to treatment. It also acknowledged that

animal models can present similar physiological responses to the far-forward treatment interval in which the wounded combatant awaits evacuation to surgical care. To this end, the expert panel recommended that preclinical studies include non-anesthetized models to study hemorrhage alone and an anesthetized model to study uncontrolled hemorrhage plus trauma in two species of large animals with hypotensive resuscitation during prolonged periods. Preclinical studies should measure short-term survival during conditions that simulate delayed evacuation to surgical care, end organ damage, and long-term survival.

The number of patients and documentation required for FDA clinical efficacy testing preclude testing resuscitation products in combat situations. However, a situation that is relevant to combat inflicted hemorrhage is all too common in the United States. Blunt trauma, such as an extremity injury from a motor-vehicle accident, is the most frequent type of civilian traumatic injury in the United States. Thus, the expert panel considered the use of experimental resuscitation products by civilian emergency medical technicians to treat extensive blunt trauma as the best surrogate model for treatment of combat-inflicted hemorrhage. Important clinical measures include coagulation profile, neurological status, end organ failure, and survival to 28 and 60 days.

Having an obligatory research proposal format encourages offerors (applicants) to submit sufficient relevant information within reasonable page limits. This also serves to limit the burden of peer-review and set a consistent standard for all submissions. Of particular importance for assessing military relevance is the recommendation for the sponsor to define and prioritize the minimal and optimal product performance goals (*i.e.*, requirements) for the offeror, and for the offeror to characterize their product as recommended by this expert panel.

Competitive product development is strengthened by scheduled gate reviews in which decisions are made to advance or halt investigations. The expert panel recommended a maximum of two years funding for preclinical studies and a maximum of three years funding for clinical studies, with the potential for continuation of funds if the project is on track and successful.

NEXT STEPS

This report provides a framework for reviewing research on novel resuscitation products that can be implemented by the sponsor. (See Chapter IV.) Implementing and developing this framework could make substantial progress in assuring that the sponsor receives high quality research proposals of sufficient military relevance that lead to products with the potential to substantially improve resuscitative care in combat and save the lives of U.S. soldiers and marines.

Editor's Note:

For further information about this study, see "Resuscitation Fluids for Use in Combat" at: <http://www.lsro.org>

I. INTRODUCTION

I.1 OVERVIEW

I.1.1 Scope of work

I.2 MILITARY PROGRAM OF RESUSCITATION FLUID RESEARCH

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I.4.1 Establishing safety and efficacy

I.4.2 Example of challenges to product development: hypertonic saline dextran

I.5 SUMMARY

I. INTRODUCTION

This report provides an overview of the military program of resuscitation fluid research and its effort to develop optimal therapies for resuscitating casualties on the battlefield. The report also examines issues involved with developing a resuscitation fluid for military use that could reasonably obtain U. S. Food and Drug Administration (FDA) approval.

The U.S. Army Medical Research and Materiel Command (USAMRMC) and the Office of Naval Research (ONR) (*i.e.*, the sponsor) asked the Life Sciences Research Office, Inc. (LSRO) to survey resuscitation fluids and adjunct therapies under development that have the potential for use in combat and to independently review research preproposals of these products. Furthermore, LSRO was to provide guidance concerning which data and criteria are needed to review proposals of experimental resuscitation products submitted in the future.

I.1 OVERVIEW

In recent years, U.S. soldiers wounded in combat have received surgical care within as little as one hour or in excess of 17 hours, depending on terrain, weather, and military situation. Future combat scenarios may require that small groups of soldiers be dispersed across large expanses of austere terrain or in urban territory, making it probable that there will be instances where medical personnel are not immediately available to treat the wounded, and evacuation is prolonged. On the battlefield, combatants who are bleeding sufficiently to compromise perfusion of vital organs require immediate medical attention by a fellow combatant with the ability to administer resuscitation fluid and hemostatic agents. Under difficult circumstances and with minimal medical training, these advanced first-responders are expected to attempt to stop any life-threatening external hemorrhaging and administer resuscitation fluid, which they carry in limited supply. Much of the information on military resuscitation care and research in this chapter was provided in presentations by the sponsor to the expert panel on January 10, 2005, supplemented with information obtained by LSRO from the published literature. (See Appendices A and D.)

The sponsor seeks new products for use as resuscitation fluids and adjunct therapies to reduce combat casualty morbidity and mortality. Technologies that enhance oxygen delivery to the tissue and/or minimize inflammatory responses are examples of strategies that have the potential to improve resuscitation outcomes. An ideal candidate for resuscitation will support the life of the casualty during an extended evacuation process, especially in conjunction with the low-volume resuscitation methods used in far-forward battlefield scenarios.

Resuscitation fluid development and resuscitation research are ongoing. There are several therapeutic products for resuscitation currently available (FDA approved), a few products in FDA approved clinical trials, and many others in preclinical evaluation. The sponsor desires a better understanding of these products as well as advice on criteria to evaluate the utility of potential technologies in order to identify and prioritize those technologies that most warrant an investment of sponsor resources.

I.1.1 Scope of work

The study described in this report was a two-phase project. During Phase I, LSRO conducted a survey of existing technologies and developing products for use in resuscitation. Monitoring devices and devices that assist fluid resuscitation were excluded as they fall outside the scope of work. Preproposals for advanced first-responder resuscitation fluid (AFRRF) were reviewed for military relevance and scientific merit. The review sought to identify experimental therapies that had the potential to meet military requirements and that warranted the further review of full research proposals.

Phase II examined processes and forms currently in use by the military and other federal programs for the review of scientific research. Recommendations were made for an effective program to further evaluate and prioritize current and future resuscitation technologies and to improve the military relevance of future proposed products and experimental models.

An independent panel of experts was given the responsibility of establishing review and ranking criteria, evaluating and ranking individual preproposals, and suggesting a framework for a research program to examine resuscitation technologies and products. The members of the expert panel were selected by LSRO for their knowledge and expertise in relevant fields, such as experimental and clinical traumatic hemorrhagic shock, resuscitation fluids, pharmacology, military casualty medicine, and the immunomodulation of shock and sepsis. (See Appendix A.)

I.2 MILITARY PROGRAM OF RESUSCITATION FLUID RESEARCH

In order to advance resuscitation in the combat environment, the military funds research into the composition and administration of resuscitation fluids, pharmacologic adjuncts to resuscitation fluids, and drugs or strategies that could sustain the casualty in the absence of resuscitation fluids. USAMRMC's resuscitation research program is managed by the Combat Casualty Care Research Program (2005) at the Walter Reed Army Institute of Research. ONR's program is managed by the Combat Casualty Care and Management Directorate at the Naval Medical Research Center (2005a). Resuscitation science research is also conducted at the U.S. Army Institute of Surgical Research and through extramural grant funding at a number of universities and research institutes.

USAMRMC and ONR have been collaborating on a life-sustaining strategy for casualties, especially those who are expected to experience long delays before evacuation to surgical care. The goals of civilian resuscitation are to save lives during emergency care and to reduce subsequent morbidity, often indicated by the incidence of late-stage organ failure. Military resuscitation is conducted in situations where the delay to reach the hospital can be hours long and the volume of fluid available for infusion could be a quarter or less of the volume lost. Thus, a successful product for military resuscitation would increase the rate of survival of casualties in the pre-hospital period (*i.e.*, decrease the killed-in-action rate) and prevent late morbidity despite the limitations imposed by the military situation.

In its effort to promote research on resuscitation fluids and to advance the application of resuscitation science in clinical practice, the Department of Defense (DOD) collaborates with other federal agencies and the medical community. For example, ONR sponsored a committee of the National Academy of Sciences to focus on fluid resuscitation for combat casualties (Institute of Medicine, 1999). This and other such activities are listed in Figure I.1.

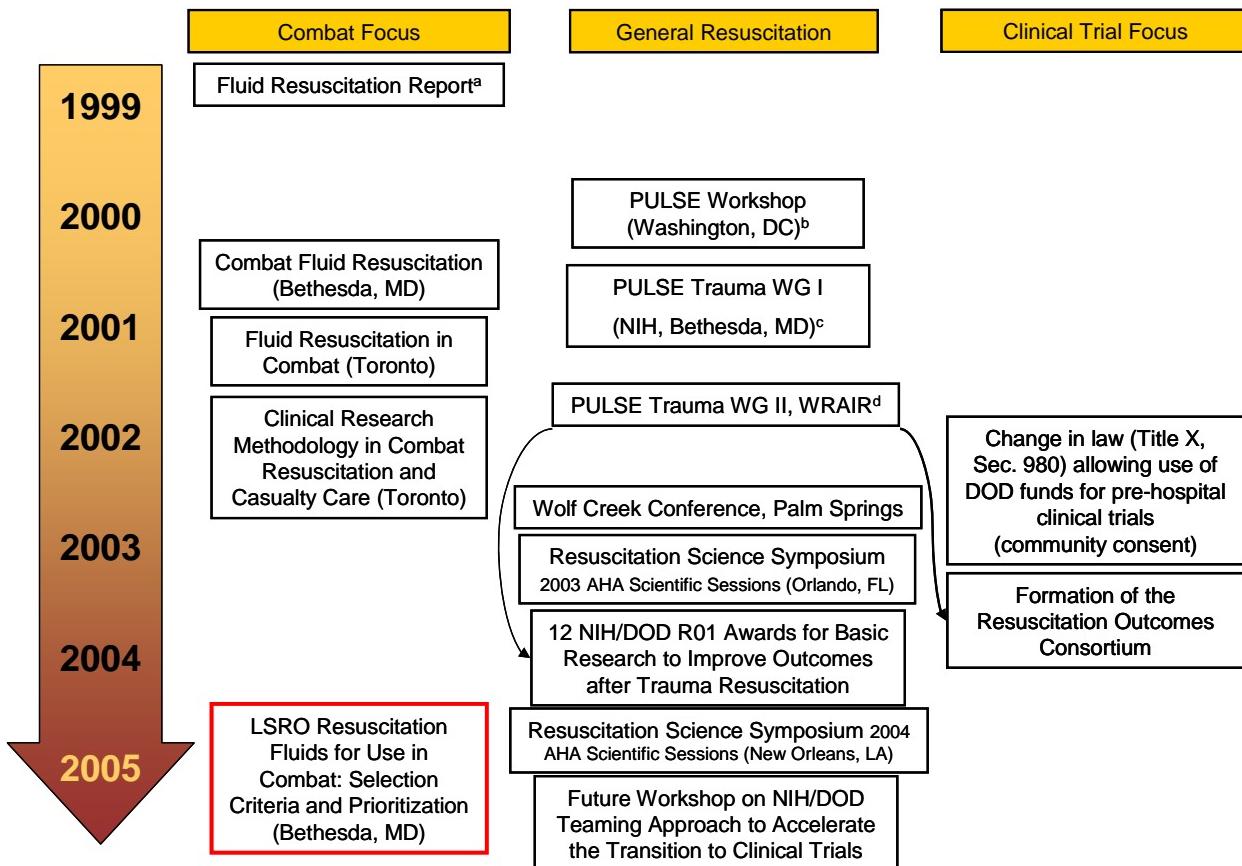


Figure I.1 Prior resuscitation science meetings and collaborations. AHA: American Heart Association; DOD: Department of Defense; NIH: National Institutes of Health; PULSE: Post-Resuscitative and Initial Utility in Life Saving Efforts; WG: Work Group; WRAIR: Walter Reed Army Institute of Research. a. Institute of Medicine, 1999 b. Weil *et al.*, 2001 c. Becker *et al.*, 2002; Carrico *et al.*, 2002a, 2002b d. Hoyt *et al.*, 2004.

Credit: E. Barrows and J.L. Atkins.

In 2000, researchers in cardiopulmonary resuscitation and trauma resuscitation came together for the Post-Resuscitative and Initial Utility in Life Saving Efforts (PULSE) initiative. This initiative was a result of considerable collaboration between the National Institutes of Health's (NIH) National Heart, Lung, and Blood Institute, National Institute of Child Health and Human Development, National Institute of General Medical Sciences, and National Institute of Neurological Disorders and Stroke, together with the Center for Devices and Radiological Health of the FDA, the American Heart Association (AHA), the American College of Cardiology, and DOD (Becker *et al.*, 2002; Weil *et al.*, 2001). It created an interdisciplinary forum for discussing novel life-saving treatments for cardiac, hypoxic, and traumatic arrest. It was further expected that the PULSE initiative would help identify the most promising new directions in cardiopulmonary and trauma resuscitation research. A growth of interest in developing resuscitation science led to:

- NIH funding of 12 basic science grants (RO1 research project grants) in 2002
- Recommendations to NIH for the implementation of the PULSE strategic plan to support resuscitation science research. These recommendations were published by the Trauma Work Group (Becker *et al.*, 2002; Carrico *et al.*, 2002a, 2002b; Hoyt *et al.*, 2004)
- Establishment in 2003 of an annual Resuscitation Science Symposium at AHA Scientific Sessions
- Formation of the Resuscitation Outcomes Consortium to test promising therapeutic strategies in multi-center trials studying cardiopulmonary arrest and severe traumatic injury, with a focus on interventions in the pre-hospital and early hospitalization phase of care (National Heart, Lung and Blood Institute, *et al.*, 2005)

The militaries of the U.S. and Canada also organized several conferences to develop a reasonable strategy for resuscitation in combat (Champion, 2003). (See Figure I.1.) These conferences led to a consensus approach to resuscitation in combat and to the current project.

I.3 RESUSCITATION FLUID USE IN COMBAT

The goal for the use of resuscitation fluid is to achieve adequate tissue perfusion by optimizing cardiac output and the oxygen-carrying capacity of the blood (Zajtchuk *et al.*, 1991). Another desired effect of this therapeutic effort is to correct metabolic disturbances that have potentially detrimental consequences (Dubick & Wade, 1994).

Resuscitation fluids that may be appropriate for a civilian population, who typically receive physician-directed emergency care within one hour of injury, may not be optimal or feasible for treating combat casualties. The optimal fluid for resuscitation of wounded military personnel must not only meet medical need but must also conform to the constraints that battlefield logistics and the physical environment impose.

I.3.1 The injured combatant

Injured military personnel differ from civilian trauma patients in that, as a group, they are younger, more physically fit, and have less incidence of chronic disease, which gives them the best chance of overcoming injury. However, in contrast to most civilian circumstances, combatants may have to endure a prolonged period of minimal care until evacuation to surgical treatment. Delayed evacuation increases the risk of dehydration and jeopardizes the wounded combatant's ability to recover.

I.3.1.1 Combat-inflicted hemorrhage

Combat casualties often have combination injuries that lead to hemorrhage. Most cases of lethal hemorrhage result from injury to the torso. Life-threatening hemorrhage is frequently caused by bullets (typically from automatic high-velocity small arms) and fragments from exploding munitions (*e.g.*, grenades and improvised exploding devices). Hemorrhage was the mechanism of death for 20% to 50% of wounded soldiers who perished in past conflicts and is considered to be the single major cause of death in the potentially salvageable battlefield casualty (Chambers *et al.*, 2005; Champion *et al.*, 2003; Institute of Medicine, 1999; Zajtchuk *et al.*, 1991). Hemorrhage from wounded limbs has accounted for nearly one-tenth of all combat deaths, yet a portion of these fatalities were preventable had appropriate pre-hospital care been provided (Champion *et al.*, 2003).

As blood is lost, blood pressure falls. Humans are likely to experience hypovolemic shock if hemorrhage depresses systolic blood pressure to less than 85 mmHg. Once blood volume is reduced by 60% or more and systolic blood pressure falls to less than 50 mmHg, irretrievable loss of consciousness and death is likely to follow (Champion *et al.*, 2003). Hoyt (2003) estimates that blood volume in a 70-kg individual is 70 mL/kg or approximately five liters total. If the soldier were to bleed at 25 mL/min (1.5 L/h) as might occur with liver or spleen injury, then hypotension is likely by one hour followed by death within two hours. A greater rate of bleeding, such as from a vascular injury producing blood losses of 100 mL/min (6 L/h), would result in hypotension within 15 minutes and death within 30 minutes. Resuscitation strategies that intercede to restore partial blood volume may help prevent death (Hoyt, 2003).

I.3.1.2 Prolonged evacuation

Substantial delays in medical evacuation can be caused by continued active engagement with hostile forces, limited control of airspace, unfavorable troop position, concealment from enemy detection (night evacuation), and poor weather. During the first phase of Operation Iraqi Freedom, the time from wounding of marines to arrival at a Forward Resuscitative Surgery System ranged from 15 minutes to 40 hours, with a median time

interval of one hour (Chambers *et al.*, 2005). Evacuations from urban environments are especially difficult. During urban conflict in Mogadishu, Somalia, casualty evacuations were delayed for approximately 15 hours because of the threat of attack and an inability to land helicopters in the narrow streets. Ground evacuation was difficult because of roadblocks, ambushes, and hostile fire. While awaiting evacuation, conditions on the ground in nearly 100°F heat with a maximum of two canteens (2 quarts) of water predisposed personnel in Mogadishu to the stress of dehydration in addition to hemorrhage (Butler, Jr. *et al.*, 2000).

Future combat scenarios are expected to involve a diffuse and dispersed battlefield for tactical reasons (Johnson & Cecchine, 2004). In this scenario, a medic may not be able to reach the casualty immediately, and soldiers would be essentially independent of medical resupply and a means of evacuation for some period. The possibility of prolonged evacuation necessitates use of resuscitation fluid by advanced first-responders in treating the wounded.

I.3.2 Administration of resuscitation fluid in combat

Due to the potential lethality of severe hemorrhage, it is imperative that medical care be provided as soon as possible after wounding to stabilize the cardiovascular system and support adequate tissue oxygenation.

The military experience in Mogadishu, Somalia showed that civilian pre-hospital care is not necessarily appropriate for a military setting (Butler, Jr. *et al.*, 2000; Holcomb, 2003). The use of resuscitation fluid on the battlefield must be straightforward, taking into consideration the difficulty that fellow combatants or medics with limited training and minimal diagnostic information will experience when treating wounded personnel on the scene and during evacuation.

I.3.2.1 Access

Intravenous access is used: (1) for patients expected to require future intravenous administration of drugs (*e.g.*, pain medications, antibiotic therapy) as is generally typical for those patients with injuries requiring that they be evacuated lying down; (2) for hydration (*e.g.*, normal saline to patients for dehydration, heat stroke), and (3) for the delivery of resuscitation fluid to patients with hemorrhage.

Once the caregiver is out of immediate danger of enemy fire, venous access is started using a saline lock with an 18-gauge catheter (Holcomb, 2003). Rarely, for some Special Operations units, intravenous access is established before combat (Cloonan, 2003). As much as one liter of solution could be administered through a 2-inch, 18-gauge catheter in approximately 17 minutes without supplemental bag-pressure compared to approximately 11 minutes with a 2-inch, 16-gauge catheter (Butler, Jr. *et al.*, 1996).

Currently, there are limited alternatives to intravenous access for infusion of resuscitation fluid. Subclavian and internal jugular venipunctures are not appropriate on the battlefield because of the potential complications from these procedures (Butler, Jr. *et al.*, 1996). Intraosseous delivery systems have been used with limited success, at least for single dose infusions of hypertonic saline dextran (HSD) under experimental conditions in animals (Dubick & Wade, 1994; Dubick & Atkins, 2003). However, intraosseous infusion of two or more boluses of 7.5% hypertonic saline into the right hind leg of swine causes localized soft tissue necrosis or bone marrow necrosis (Alam *et al.*, 2002).

I.3.2.2 Consensus approach

Resuscitation efforts are aimed at expanding blood volume to perfuse vital organs. This effort to thwart lethal effects of hemorrhage must be tempered to avoid the potentially fatal consequences of overly aggressive volume expansion. For example, resuscitation efforts to normalize blood pressure could dislodge primary clots and precipitate re-bleeding from sites that had ceased hemorrhaging (Butler, Jr. *et al.*, 2000; Consensus

Working Group on Pre-hospital Fluids, 2001). Although the question is still open as to the best approach to resuscitation, the military has had to establish a working protocol that would facilitate care under difficult conditions. Military physicians, civilian trauma physicians, and physicians with vast field experience working with the Red Cross and Doctors Without Borders (*Médecins Sans Frontières*) have endorsed the use of an initial period of hypovolemic resuscitation for the pre-hospital trauma care of uncontrolled severe hemorrhage, with the presence of a palpable radial pulse as an endpoint for the initial resuscitation (Butler, Jr. *et al.*, 2000).

In 2001, a conference co-sponsored by USAMRMC, ONR, and the Uniformed Services University of the Health Sciences generated consensus recommendations for resuscitation of non-head-injured combat casualties (Champion, 2003). These recommendations are grounded in the need for hemorrhage control, optimization of fluid use, and selection of endpoints for resuscitation that are obtainable by the front-line medic in noisy and chaotic military pre-hospital situations (Holcomb, 2003). Consistent with these recommendations, the military initially uses a hypotensive resuscitation strategy to treat uncontrolled severe hemorrhage on the battlefield. For non-head-injured combat casualties, low volume administration (*e.g.*, 250 to 500 mL) of fluid is titrated while monitoring the casualty's response until they display one of the following:

- Palpable radial pulse
- Ability to demonstrate cognitive activity (*e.g.*, responds lucidly to command for name, rank, serial number)
- Sustained systolic blood pressure of 85-90 mmHg (if measure is available).

In practice, soldiers and marines are infusing 500 mL of fluid and checking the patient for signs that the infusion is having an effect. If the casualty is unresponsive, a maximum of 500 mL more fluid is administered. The military strategy does not meet the standard of Advanced Trauma Life Support® that is used in the U.S. civilian population. In particular, the military does not use the civilian replacement ratio of 3:1 intravenous fluid to blood lost and immobilization of the cervical spine using a hard neck collar is not practiced on the battlefield.

The patient with a head injury may require a higher systolic blood pressure to maintain cerebral perfusion and reduce secondary brain injury (Revell *et al.*, 2002). Hence, the initial use of hypotensive resuscitation is not recommended for combatants with head injury (Butler, Jr. *et al.*, 2000; Holcomb, 2003). In practice, the advanced first-responder may not be able to discern whether or not the patient has a head injury and is typically unable to measure systolic blood pressure (Holcomb, 2003). Therefore, there is a risk that a head trauma patient administered resuscitation fluid could experience fluid overload when cognitive function is used as an endpoint for resuscitation. For patients who sustain traumatic brain injury, redistribution of fluid volume from the vascular space into the extracellular compartment may increase cerebral swelling and increase intracranial pressure leading to a reduction in brain blood flow (Wade *et al.*, 1997). Biomonitoring devices to measure parameters such as cognitive state, blood pressure, and hydration are currently under development, but are several years away from battle-readiness (Lewis, 2004).

Two of the more critical outcomes observed at combat support hospitals after hypotensive resuscitation and prolonged evacuation are that some soldiers arrive cold and coagulopathic, and others, who are lucid and medically stable upon arrival, destabilize with fatal consequences during full resuscitation to normal blood pressure. Consensus agreements are a starting place for clinical practice, but best practice requires obtaining evidence of the optimal degree and maximal duration of hypotension for survival. Additional data from hypovolemic resuscitations are needed to further evaluate the benefit of this approach for military use.

I.3.2.3 Product selection

The military market is not sizeable enough to support the production of a military-specific product, particularly during non-war years. Hence, the military must select a resuscitation product from what is available in the commercial sector, relying on the civilian market to maintain product supply.

In general, military policy precludes the medical use of any drug that has not been approved by the FDA. Separate formulations, if combined into one product, require additional testing and FDA approval (Dubick & Bruttig, 1996).

Fresh whole blood is not a suitable option for battlefield resuscitation because of the challenges for supply, conditions of storage, and need for type-matching. In far-forward battlefield conditions, colloid or colloid-and-crystalloid fluids are used for resuscitation by advanced first-responders. At aid stations and forward surgical settings, isotonic crystalloid fluids are used. For its colloid solution, the military is currently using a 6% hetastarch solution (Hextend[®]) to maximize blood volume expansion per unit weight of product administered with an eye toward maintaining as favorable a coagulation profile as possible. As discussed in section I.3.3.2, combat lifesavers carry crystalloid fluids (*i.e.*, normal saline or lactated Ringer's solution) in limited supply and medics typically carry two-liters each of Hextend[®] and normal saline.

The goal of resuscitation for treatment of acute hemorrhage is to facilitate volume expansion with restoration of tissue perfusion, and thereby oxygen delivery, to prevent or delay the onset of hypovolemic shock (Champion, 2003). An optimal fluid should remain primarily in the vascular space to expand and maintain blood volume rather than infiltrate the extracellular space (Consensus Working Group on Pre-hospital Fluids, 2001).

Resuscitation fluids have varying effects on the expansion of blood volume. Pearce and Lyons (1999) suggested that use of lactated Ringer's solution to replace lost blood volume would require a volume of at least four to five times that of the lost blood volume. In contrast, less colloid solution would be needed for a comparable blood expansion. For example, one hour after infusion, a liter of lactated Ringer's solution is expected to expand intravascular fluid volume by approximately 250 mL, whereas infusion of one 500 mL bag of hetastarch (*e.g.*, Hespan[®]) is expected to expand intravascular fluid volume by approximately 800 mL. Hence, use of hetastarch might achieve a three-fold advantage in volume expansion with only one-half the weight requirement of lactated Ringer's (Holcomb, 2003). Similarly, it was projected that low-volume (250 mL) HSD or colloid administered over a period of 15 minutes could amount to 750 to 850 mL volume expansion over a period of 30 minutes (Champion *et al.*, 2003). Holcomb (2003) suggested that no more than 1,000 mL of Hextend[®] should be given to any one casualty, resulting in an intravascular expansion that he calculated to be approximately equivalent to that from six liters of lactated Ringer's solution.

In the long term, one or more products that can obtain FDA approval are needed for resuscitation. Optimally, these products in combination with early and appropriate care would reduce the number of combatants who are killed-in-action and mitigate post-resuscitation morbidity.

I.3.3 Constraints on type of product and product use

There are many constraints on the resuscitation of wounded combatants. These include an austere and dangerous environment, the frenetic pace of battle, limited medical training of the advanced first-responders administering treatment, and limitations in the amount and types of treatments available in far-forward situations.

I.3.3.1 Echelon-based medical support and constraints on product use

The mission of the military medical service is to conserve and maintain the fighting power of the command by returning wounded combatants to duty. In a theatre of military operations, troops are organized into operational units of increasing inclusiveness, with varying medical capabilities corresponding to unit size. Military casualties are evacuated through successive echelons of increasingly comprehensive and sophisticated care (Appendix E) (Zajtchuk *et al.*, 1991). Each medical unit does what is necessary either to return the casualty to duty or to evacuate the patient to the next most comprehensive echelon for further treatment (Zajtchuk *et al.*, 1991). Battalion Aid Stations are staffed by a physician or physician's assistant (Cloonan, 2003). General

surgeons are available in the forward surgical team and neurosurgeons are intermittently available at the combat surgical hospital. Intensive care units are also available at the combat surgical hospital.

The traditional system of phased medical support in a battlefield environment begins with the combat medic or combat lifesaver at the front line. Combat medic training is conducted in a 16-week “91W” program at Fort Sam, Houston, Texas. Except in the Special Forces, medics are not trained to the level of a civilian emergency medical technician. One combat medic is allotted per platoon of 40 soldiers (Cloonan, 2003). Combat medics may be absent from particular maneuvers or may be located some distance away from the wounded, such as in another vehicle that is unable to divert from the mission at hand (Johnson & Cecchine, 2004). Therefore, the U.S. Army also trains roughly one of every five combat troops or one individual in every combat vehicle as a combat lifesaver. The combat lifesaver course is typically three days in duration and includes instruction in administration of intravenous fluids (Cloonan, 2003). The combat medic and the combat lifesaver are trained in tactical medicine principles that differ from civilian medical training. Thus, the first responder who responds to care for emergent bleeding casualties during combat missions might be a medic or fellow combatant with a minimal level of medical proficiency.

Field medical units and personnel in the first echelon of care are subject to enemy attack, often requiring crowded conditions in foxholes and other shielded areas. Furthermore, there may be mass casualties requiring simultaneous care, so care must be provided as expeditiously as possible once the care-giver is safe from enemy fire.

There is an increased risk of complications from treatment given on the battlefield compared to treatment under more controlled circumstances. Non-sterile field conditions raise the risk for infection. It may not be possible to warm fluids prior to administration, increasing the risk of hypothermia-induced coagulopathy (Consensus Working Group on Pre-hospital Fluids, 2001). In the past, high error rates in the medical information imprinted on identification tags, such as error of ABO group and Rh type, increased the risk for administration of unsuitable blood products (Joseph, 1995). Adverse reactions to resuscitation fluid (*e.g.*, anaphylaxis) are difficult to remedy on the battlefield, and iatrogenic problems arising from improper and/or unnecessary cannulation and administration of fluids are also possible. In combat medical emergencies, it is also possible that a care-giver will fail to prioritize treatment, administering resuscitation fluid when the patient requires other life-saving actions (Cloonan, 2003).

The patient’s positioning under makeshift conditions, environmental factors such as extreme heat or cold, and altitude could influence physiology and response to treatment. Additional stressors on the delivery of care may be encountered during evacuation: for example, transportation-related complications could occur if the treatment and/or patient being infused are negatively affected by the cold and pressure conditions of military helicopter evacuation. As non-pressure controlled aircraft ascend, the barometric pressure falls and the availability of oxygen declines, which leads to reduced tissue oxygenation. Conditions on military helicopters during evacuation are windy, with dust, grit and grime propelled onto all surfaces.

I.3.3.2 Constraints on product durability and size

Products used in combat are subject to variable conditions that could compromise the identity, quality, purity, strength, and composition of the product. Because there are no controlled refrigeration or storage conditions on the battlefield, products can be subjected to environmental extremes ranging, for example, from blistering plains in Iraq to freezing mountains in Afghanistan. Moreover, because resupply is unpredictable, products which are not field-stable for long periods have limited value. In addition, products pre-packaged for inclusion in medical replenishment supplies may have to withstand being air-dropped (Butler, Jr. *et al.*, 2000).

Combatants are widely dispersed across the battlefield for tactical reasons. Aid stations, even if in the area of the wounded, are small and their supply of medical products, such as intravenous catheters, gloves, and

resuscitation fluids, is limited. Hence, these medical supplies may only be accessible to the advanced first-responder if they are carried in the soldier's gear. Combatants typically carry or wear 40-60 kg (90-130 lb) of equipment into battle areas (Champion *et al.*, 2003). Often they will rid themselves of any supplies, including medical supplies, they deem to be not vital to their mission. Among their other gear, combat lifesaver soldiers pack two 500 mL bags of normal saline or lactated Ringer's solution (Cloonan, 2003). Combat medics, the resupply point for the combat lifesaver, typically carry four liters of resuscitation solution, but have been known to carry up to six liters, as six one-liter or twelve 500 mL bags of fluid (Holcomb, 2003).

These environmental and battlefield constraints pose challenges to the design of useful resuscitation fluids and suggest that military requirements would include consideration of product weight, volume, stability, durability, ease of use, and safety of use across a spectrum of potential scenarios.

I.4 PREVIOUS EXPERIENCE WITH DEVELOPMENT OF MILITARY RESUSCITATION FLUID

For the past twenty years the military has been working with the trauma medical community to develop safe and effective resuscitation fluids that can obtain FDA approval. The military's goal is to develop a resuscitation fluid and/or adjunct therapies that will increase the number of combatants who survive uncontrolled severe hemorrhage. A historical perspective on the development of military resuscitation fluid is instructive to the future framework of such efforts in that it reveals challenges posed by the unique conditions of use and some continuing gaps in resuscitation science.

Current resource-investment estimates by USAMRMC for developing a single medical product (in general) are \$17.1 million to conduct a 2-year-long Phase I trial, \$24.4 million to conduct a 3-year-long Phase II trial, and \$21.7 million to conduct a 3-year-long Phase III trial (Stewart *et al.*, 2002). Total financial outlay for development of a single product, including long-term animal studies, processing for FDA approval, and additional overhead, is approximately \$78 million, which does not include any product purchase or manufacturing costs.

I.4.1 Establishing safety and efficacy

There are no FDA-approved products for the specific indication of resuscitation for hemorrhagic shock, as this would be too limiting an indication. Resuscitation fluid products used to treat hemorrhagic shock have received FDA approval for broader treatment categories, such as treatment for hypovolemia for the product Hextend®. The FDA is in a systematic and protracted process of reviewing the effectiveness of treatments that obtained approval prior to the early 1960's based only on safety, such as lactated Ringer's.

Because safety and effectiveness are the pivotal issues that concern FDA in its review of new drug products, the following evidence for a new resuscitation fluid, as with other new drugs, must be provided to FDA (Farley, 1995):

- Results demonstrating that the product is safe under the conditions of use in the proposed labeling
- Results of well-controlled studies providing substantial evidence of effectiveness.

Note that FDA approval includes specification of route of delivery so that if a fluid were approved for intravenous administration, a new drug application would have to be filed to obtain approval to administer the same solution via an intraosseous or other route.

To date, military clinical trials to test new treatments have not been feasible because the number of casualties has been low and unpredictable, and the circumstances under which combatants are wounded and care is delivered have not been adequately documented and lack sufficient experimental control. However, future technologies may increase the possibility that such studies could be conducted to evaluate the scientific validity of various therapies under combat conditions. Methods are being developed to utilize electronic identification

tags, digital cameras, and thumb-drives (portable data storage devices) to capture patient information, potentially including pictures of injuries and x-rays, and transmit these data by email between medical units and for use in the Joint Theater Trauma Registry.

The military is a distinct population and would not be represented in clinical trials conducted in the civilian population. For example, civilian trauma trials, which have the advantage of rapid response by emergency medical technicians with adequate resources, do not necessarily involve the degree of hypotension experienced by the wounded combatant, or the lengths of time the military population await resuscitation and evacuation. Specifically, a Phase III trial for efficacy in trauma with delayed evacuation is not permissible in the United States. A contrast is made in Table I-1 between the circumstances expected during a controlled civilian clinical trial undertaken to obtain FDA approval for a new resuscitation fluid, and the military circumstances and challenges faced in combat use and testing.

In lieu of a military clinical trial, a potential product must be tested for a comparable indication in a civilian population. The civilian data must be supplemented with data from animal studies to justify approval for the military use. Aspects of military conditions such as prolonged evacuation have been mimicked using animal models. Animal studies can be designed to provide information on the use of experimental resuscitation fluids and adjunct therapies under extreme trauma conditions.

An experimental product will have to present a very low risk of any adverse effect in order to obtain approval for testing in a civilian pre-hospital population. In contrast, military selection and acceptance from among FDA-approved civilian products of one for use in combat might tolerate a greater risk of short-term problems than that permitted for testing in civilians if the chance for long-term survival of the combatant is improved over standard military care. It is recognized that increased survival could be accompanied by increased morbidity among survivors.

Table I-1 Comparison of controlled civilian clinical trials of resuscitation products and their use and post-market surveillance in combat.

Factor	Civilian clinical trial	Use and post-market surveillance in combat
Pre-hospital setting	Suburban and urban areas	Far-forward front line
Population	Civilians (diverse age, medical history, physical fitness, use of illegal drugs and alcohol)	Soldiers and marines are less heterogeneous than civilians
Hemorrhagic injury	Multiple blunt trauma, some penetrating trauma, some concurrent with neurotrauma; injuries are well-diagnosed	Penetrating trauma from bullets or flying fragments, initially not completely diagnosed (e.g., head injuries)
Personnel and resources	Trained Emergency Medical Technician and team; well stocked supplies and equipment; in communication with physician-directed center; back-up personnel available; Advanced Trauma Life Support® protocols	Minimally trained advanced-first responder and/or combat medic; limited supplies, equipment, communication, and back-up
Product selection and approval	Community consent and approval by an institutional review board is required for use of experimental products. Selection of products is based on safety and efficacy. Wide-ranging product requirements, (e.g., temperature control, shelf-life) can be accommodated.	Products must have U.S. Food and Drug Administration approval for similar indication. Selection of products is based on safety, efficacy, and a battery of logistical limitations. There are few, if any, options for alternative treatment
Evacuation from scene to surgical care	Evacuation (minutes) by vehicle/aircraft on scene and waiting	Evacuation (hours/days) by any means necessary through successive echelons of care
Patient data from scene	Retained; paper trail	Data capture is a low priority; often not available
Outcome measures	Survival outcome, secondary biomarkers (e.g., organ failure), surrogate measures (e.g., days of ventilation, duration of hospital stay, cost of care)	Survival outcome and logistical advantages
Oversight from research team	Urban academic center located within minutes of accident scene and the delivery of patient critical care	Oversight location remote from scene and critical care

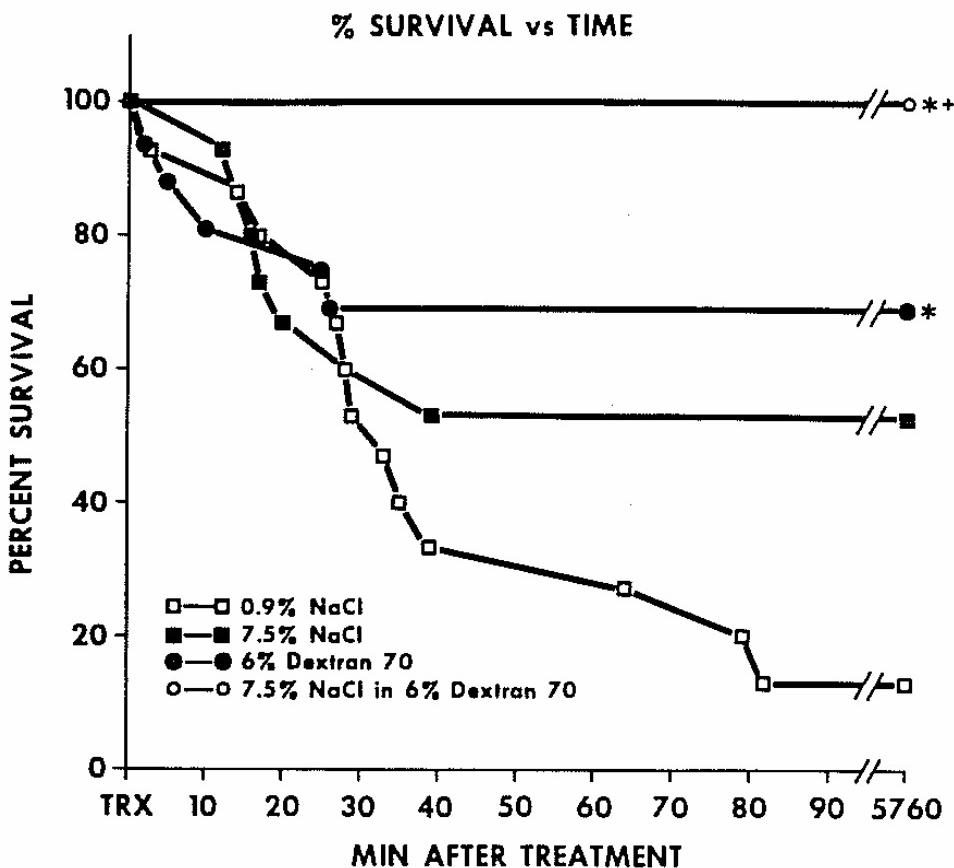


Figure I.2 Survival outcome after an 11.5 mL/kg infusion of treatment solutions. TRX: end of treatment. *Significantly different from 0.9% NaCl-treated animals ($p < 0.001$). +Significantly different from 7.5% NaCl-treated animals ($p < 0.01$). (Reprinted from *Annals of Emergency Medicine*, Vol. 15, Maningas, *et al.*, Small-volume infusion of 7.5% NaCl in 6% Dextran 70® for the Treatment of Severe Hemorrhagic Shock in Swine, pp. 1131-1137, Copyright 1986, with permission from The American College of Emergency Physicians.)

I.4.2 Example of challenges to product development: hypertonic saline dextran

Smith and coworkers (1985) reported formulating a hypertonic solution containing 7.5% saline and 6% dextran 70. This HSD solution was able to restore cardiac output within three minutes in hemorrhaged sheep and sustained a significantly higher cardiac output over a three-hour observation period compared to several other solutions tested. The improvements in relevant biomarkers from HSD were repeated in several animal models (Kramer, 2003). More importantly, it was demonstrated that HSD significantly improved animal survival compared to treatment with normal saline or other hypertonic saline solutions (Figure I.2) (Kramer, 2003; Maningas *et al.*, 1986). Reports that HSD enhanced survival in hemorrhaged animals and the logistical advantage it offered of reduced weight burden by providing a high blood-volume expansion for the volume administered provided an impetus for further product testing of efficacy and safety (Dubick & Wade, 1994; Kramer & Holcroft, 1990; Tølløfsrud *et al.*, 2001).

Toxicological studies of HSD, as required by FDA, were undertaken in mice, rabbits and dogs to evaluate dose response when HSD was given as a single bolus at up to five times the recommended dose and when administered daily for up to 14 days (Dubick & Wade, 1994). Because HSD is administered intravenously, product safety evaluations also included investigations of the detrimental effects from inadvertent administration into the wrong compartment. Subcutaneous and intra-muscular injections of HSD were studied in mice and rabbits. Results demonstrated that if the combat medic were to miss the vein, HSD could cause a limited compartment syndrome with localized necrosis. Intraosseous delivery of HSD has achieved favorable

hemodynamic responses under experimental conditions in animals, but further investigation is needed to determine the localized adverse effects of HSD on bone tissue (Dubick & Wade, 1994; Dubick & Atkins, 2003).

More than 200 preclinical studies of HSD were conducted prior to its first human clinical study. Pharmacokinetic studies examined the distribution, clearance, and renal excretion of sodium chloride and dextran solutions in normotensive and hypotensive animals. Further safety questions concerned the effect that HSD had on plasma sodium concentration under conditions of normal hydration and dehydration, plasma protein concentration, platelet aggregation and activation, blood coagulation, and HSD interference with blood cross-matching (Dubick & Wade, 1994). Also investigated was the impact of HSD on these laboratory tests for subjects with alcohol, cocaine, or other drugs in their system.

Phase I clinical trials helped to demonstrate the efficacy of HSD in humans. Note that there are no standard methods for measuring the blood volume expansion of resuscitation therapy. Thus, a number of dilution techniques were used (*e.g.*, Evans blue dye, carbon monoxide, labeled albumin (I-125 albumin), red blood cells and/or hemoglobin, and hematocrit concentrations) (Hahn, 2002; Tølløfsrud *et al.*, 2001). Some of the initial human studies were conducted in Sweden, sponsored by Pharmacia, which at that time held a development agreement for HSD with the University of California (Kramer & Holcroft, 1990; Royal Pharmaceutical Society of Great Britain, 2004). It was demonstrated in normal subjects, who had from 72 mL to 360 mL of blood withdrawn, that HSD had the effect of a one-to-one blood volume expansion per volume infused, superior to the effect from normal saline, lactated Ringer's, or other hypertonic saline or dextran-70 solutions, with a peak effect in blood volume expansion at thirty minutes past baseline (Drobin & Hahn, 2002; Svensén & Hahn, 1997). The Phase I clinical studies confirmed the results of earlier animal studies indicating that HSD provided a sustained expansion of blood volume. One additional finding from human studies was that infusion of this hypertonic fluid can cause an intense feeling of warmth with flushing, which was characterized as painful for some volunteers at a rate of $3 \text{ mL} \cdot \text{Kg}^{-1}$ in 30 minutes and merely unpleasant for others, who were premedicated with diazepam, when infusion was limited to $4 \text{ mL} \cdot \text{Kg}^{-1}$ in 10 minutes (Drobin & Hahn, 2002; Tølløfsrud *et al.*, 1998).

DOD had been actively involved in preclinical studies of HSD until product development reached readiness for human trials. At that time, the DOD could not perform or fund human pre-hospital clinical trials of HSD because of the restrictions imposed by 10 USC 980, which required informed consent of the subject or a legal representative of the subject in advance of treatment (Maningas, 1989; Naval Medical Research Center, 2005b; USAMMDA, 2004). Since the 2001 revision of Section 733 (Enhancement of medical product development) of 10 USC 980, it is now possible for the DOD to initiate a pre-hospital protocol and fund the development of experimental therapies for human use (USAMMDA, 2004; U.S. Congress, 2001a, 2001b).

Phase II human clinical trials conducted in the field and in emergency departments supported findings from earlier studies by showing that HSD improved biomarkers (Holcroft *et al.*, 1989; Vassar *et al.*, 1991). Improvements from HSD were measured for blood volume expansion, systolic blood pressure, cardiac output, urine output, and fluid requirements. However, the improvement in survival in these studies was not significant compared to survival with standard care. One consideration derived from studies of hypertonic fluids in cardiac surgical patients is the importance of selecting valid physiological endpoints of resuscitation to prevent fluid overload rather than using a fixed-dose infused volume as the endpoint (Kramer *et al.*, 1998).

In the first U.S. Phase III randomized, double-blind, multi-center trial of HSD, the use of either 250 mL of HSD or 250 mL of a standard resuscitation solution as the initial infusion for hypotensive trauma patients was compared (Mattox *et al.*, 1991). Subsequent resuscitation fluids were selected for administration to each patient based on the discretion of the treating physician. Survival was assessed at 24 hr. Interim safety data analyses were conducted after accrual of 422 patients (211 patients per treatment) of the planned 700 total patient enrollment. Survival at 24 hr was not significantly different between groups (88% for the HSD group and 82% for the standard group), failing to support the efficacy of HSD treatment under these conditions of use. Once it

was determined that more than 1200 patients would be required to detect a significant difference between groups the study was terminated (Mattox *et al.*, 1991). This multi-center trial was supported in part by Pharmacia AB (Uppsala, Sweden) and Pharmacia, Inc. (Piscataway, NJ), which did not renew its development agreement for HSD with the University of California. Phase III trials such as this are costly, estimated to range from \$10 to \$25 million for direct costs, data management, monitoring, and medical oversight.

A later analysis of data collected from the multi-center trial of HSD revealed improved survival to discharge with HSD compared to normal saline for those patients with hemorrhage and hypotension from gunshot or stab wounds to the torso and who required surgery (Wade *et al.*, 2003). For the group treated with HSD, systolic blood pressure significantly increased an average of 27 mmHg, raising the possibility of increased bleeding. However, fluid requirements over the subsequent 24 hours did not differ between groups receiving HSD or normal saline (Wade *et al.*, 2003). Human studies thus far have shown that estimated blood loss and blood replacement in patients given hypertonic solutions are no greater than for those given isotonic solutions (Mattox *et al.*, 1991; Wade *et al.*, 2003).

Currently, HSD is not approved by FDA for use as a resuscitation fluid for trauma or surgery because U.S. trials failed to demonstrate efficacy. There also could be concerns that a subpopulation of individuals in pre-hospital trials might even be adversely effected by HSD (*e.g.*, increased incidence of infection due to a suppression of the immune system by HSD compared to standard care). In contrast, HSD under the trade name of RescueFlow® is approved in 14 European countries for use as a small volume resuscitative fluid for treatment of extensive hemorrhage (RescueFlow®, 2005).

The Resuscitation Outcomes Consortium is currently planning two multi-center trials of hypertonic resuscitation fluid in two populations of trauma patients, to be conducted simultaneously using similar interventions and infrastructure (National Heart, Lung and Blood Institute, *et al.*, 2005). Both studies will be three-arm, randomized, blinded intervention trials comparing HSD, hypertonic saline alone (7.5% saline), and normal saline as the initial resuscitation fluid administered. Study 1 seeks to determine the impact of hypertonic resuscitation fluid on survival for blunt or penetrating trauma patients in hypovolemic shock. Study 2 seeks to determine the impact of hypertonic resuscitation fluid on long-term (6 month) neurological outcome for blunt trauma patients with severe traumatic brain injury.

The history of HSD reveals the substantial body of data that must be generated to document the safety and efficacy of new resuscitation fluids. Generation of data for product development through FDA approval requires considerable commitment of time and resources. Collaboration among researchers to conduct fundamental experiments on toxicology, pharmacology, and pharmacokinetics in animal and human subjects is not only beneficial, but is necessary for clinical trials to recruit enough subjects to discern significant differences in human survival.

I.5 SUMMARY

Traditional constraints on battlefield resuscitation such as an austere, dangerous environment, infrequent resupply, and limited medical training of caregivers impose unique requirements on the selection and design of resuscitation fluid products for combat use. Potential future constraints include a longer period of time before the medic can reach the casualty and a prolonged wait for medical evacuation. Because resuscitation fluids used by the military must be approved by FDA, product development of new resuscitation fluids requires the commitment of considerable time and resources. Therefore, products that are relatively far along in development, that have preliminary data establishing safety and effectiveness, and that have the potential to meet logistical considerations imposed by combat conditions would be of greatest interest to the military.

II. SURVEY OF RESUSCITATION FLUID PRODUCTS WITH POTENTIAL FOR MILITARY USE

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II. SURVEY OF RESUSCITATION FLUID PRODUCTS WITH POTENTIAL FOR MILITARY USE

This chapter describes a survey that was conducted by the Life Sciences Research Office, Inc. (LSRO) to inform the sponsor of those resuscitation fluids and adjunct therapies in development and those already in the market that might be useful for advanced first-responders to treat hemorrhagic shock on the battlefield.

II.1 SURVEY METHODS AND INCLUSION/EXCLUSION CRITERIA

Submission of preproposals was invited to facilitate a survey of novel resuscitation fluid treatments and to obtain preproposals for review to identify those having merit for further review of a detailed full proposal.

II.1.1 Announcements and invitations for submission of preproposals

The sponsor posted a public request-for-information on the Federal Funding Opportunities website on August 3, 2004 (Appendix B). The initial deadline for submission of preproposals was September 7, 2004. On September 2, 2004, the public notice was modified to extend the deadline to October 29, 2004. The initial announcement was also included in the August 15, 2005, issue of the Medical Research Funding Bulletin. In addition, LSRO posted the initial announcement on its website and contacted more than 150 researchers in the military, academia, and industry. These announcements and invitations requested the submission of five-page preproposals for research on novel fluids or adjunct therapies intended for use in combat conditions. The invited individuals and companies were identified by searching PubMed and the Internet, and by locating lists of participants at resuscitation science conferences. Researchers who contacted the military directly for information on funding opportunities were directed by the military to contact LSRO.

The Advanced First-Responder Resuscitation Fluid (AFRRF) expert panel, the sponsor, and the LSRO Board of Directors were given an initial list of novel resuscitation fluids and adjunct therapies and a list of researchers who had been contacted thus far so that missing categories of resuscitation treatment might be identified prior to peer-review of preproposals. The sponsor identified several additional categories of treatment as having the potential for product development—perfluorocarbon microbubbles, pyruvate, ethyl pyruvate, free radical scavengers, melatonin, N-acetylcysteine, TEMPOL (4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl), and androstenediol—and LSRO attempted to contact investigators of these novel treatments.

In order to obtain the broadest array of novel treatments from which to select leading candidates, LSRO collected all preproposals submitted before the full expert panel began its review on March 7, 2005. Because the initial announcements and the emails to researchers stated that "*submissions received after the deadline will not be guaranteed a full review by LSRO*," it was further stated in the public announcement that submissions received after the deadline might be considered for review. It is possible that these changes may have limited or biased the submissions from offerors (applicants) who submitted a preproposal by the published deadline and did not forward additional data or relevant information that became available subsequent to their submission, and/or who would have benefited from additional time to prepare.

II.1.2 Receipt of preproposals, proprietary data, and other communications

By March 7, 2005, LSRO had received 65 preproposals for consideration. Of these, at least 43 (66 %) were from offerors whom LSRO had contacted directly by email. The remainder came in response to public notices or word-of-mouth. Of these 65, eight preproposals were received by the initial deadline of September 7, 2004, an additional 20 were received by the extended deadline of October 29, 2004, another 35 arrived by the date of the first expert panel meeting on January 11, 2005, and the final two were submitted by February 4, 2005.

Approximately 66% of offerors who submitted a preproposal had contacted LSRO prior to their submission to request information about the format for submission, the type of information to include in the preproposal, and the submission process. Five offerors called to notify LSRO of corrections to their preproposal. LSRO documented all calls and other communications in a log. LSRO received questions nearly on a daily basis from offerors wanting updates on the status of their respective preproposals. In response to these inquiries, LSRO revealed the process of the project, but did not reveal the expert panel's specific recommendations.

Provisions were made for the review of proprietary data by executing confidentiality agreements with the expert panel and by providing security arrangements for such data.

II.1.3 Preliminary description and organization of preproposals

A table of preliminary descriptions of the preproposals was prepared to apply inclusion and exclusion criteria and to assign reviewers from the expert panel to conduct the initial reviews. LSRO extracted the following information, if available, from each preproposal: title, name and affiliation of the principal investigator, treatment and placebo agents, type of subjects, and outcome measures.

II.1.4 Inclusion/exclusion of preproposals

Preproposals of novel fluids, components of fluids, and pharmacologic agents were considered for inclusion. Monitoring devices, injection devices, and other non-fluid strategies were not included. LSRO identified six preproposals that did not meet inclusion criteria. Five of the six preproposals were excluded for proposing to study a device, rather than a resuscitation fluid, a component of resuscitation fluid, or a pharmacologic agent. The sixth preproposal concerned the development of a prognostic early marker of organ failure and did not propose to study a resuscitation strategy. The sponsor was notified of the six excluded preproposals on February 4, 2005 so that the sponsor could expeditiously inform these offerors of the status of their preproposals.

II.2 SURVEY OF NOVEL RESUSCITATION FLUIDS AND ADJUNCT THERAPIES FOR USE IN COMBAT

The 59 studies under consideration proposed to test existing drugs and/or fluids as well as new agents to improve survival and reduce morbidity from combat-inflicted hemorrhage. Several proposed treatments were combination therapies that targeted one or more approaches to treating hemorrhagic shock and/or preventing subsequent morbidity.

Methods for administration of the proposed experimental fluids included: oral (enteral), sublingual, intranasal, intravenous, intramuscular, intrathecal (intraspinal), intraperitoneal, and intraosseous routes.

Preclinical models of hemorrhage and resuscitation varied substantially between preproposals. Table II-1 presents examples of the types of preclinical models and clinical subjects proposed by the offerors as relevant for the treatment of hemorrhagic shock on the battlefield. In some preproposals, the type of animal model or human subject was not specified.

The proposed treatments are grouped below by the predominant goal of therapy, as follows: blood rheology and coagulation, cardiovascular stability, oxygen delivery, cell structure and metabolism, inflammatory and immune responses, and other. Since several similar experimental fluids or agents were proposed by more than one research group, the proposed treatments listed do not necessarily represent distinct preproposals.

II.2.1 Blood rheology and mechanisms of coagulation

Seven preproposals indicated six types of treatments targeting blood rheology and mechanisms of coagulation. Testing was proposed in preclinical models and in human civilian trauma patients, including those undergoing early repair of spinal fracture or complex acetabular (hip) fracture. All treatments are administered intravenously.

II.2.1.1 Proposed treatments targeting blood rheology and mechanisms of coagulation

The preproposals include the following treatments:

1. An anti-fibrinolytic agent via direct infusion or as an additive in resuscitation fluid
2. Infusion of rehydrated, lyophilized platelets as an adjunct to resuscitation fluid
3. Human plasma concentrates, high in clotting protein, as a resuscitation fluid
4. Recombinant activated factor VII via bolus injection as an adjunct to resuscitation fluid
5. Combinations of anti-complement agents and anticoagulants as an adjunct to resuscitation fluids
6. Blood soluble, synthetic, and naturally-derived “drag-reducing polymers” as additives in resuscitation fluid used in combination with small-volume resuscitation

II.2.1.2 Proposed measures of treatments targeting blood rheology and mechanisms of coagulation

Measures of product characteristics and development include:

- Product formulation
- Pathogen inactivation during manufacture
- Effect of sterilization on stability of the solution
- Product quality control
- Product stability during storage and under varying environmental conditions simulating battlefield conditions (*e.g.*, stability assessed by loss of molecular weight, cross-linking, hydrolysis, alkylation, or product yield)
- Product biocompatibility with blood and blood products; tests of neoantigenicity of product

Treatment-specific measures include:

- Pharmacokinetics (*i.e.*, biodistribution, circulation half-life, and clearance of experimental agent from circulation)
- Total blood loss
- Transfused blood volume requirement
- Resolution of hemorrhage
- Blood coagulation profile
- Blood component integrity
- Whole blood rheology

Table II-1 Types of preclinical models and human subjects in preproposals received. These were suggested by principal investigators for investigating the treatment of hemorrhagic shock on the battlefield

Subject	Model		Variations	
Small animal (mouse, rat, rabbit)	Hemorrhagic shock	Uncontrolled	Trauma No trauma	<ul style="list-style-type: none"> • Liver injury • Lethal and small volume resuscitation • Bleed via arteriotomy punch • Crushed limb
		Controlled	Trauma No trauma	<ul style="list-style-type: none"> • 60% loss of blood volume • 50% - 60% loss of blood volume via artery • Lethal via rapid loss of 40% blood volume over 10 minutes followed by a 3-hour period of shock (to simulate delayed transport) during which another 20% of blood volume is lost via slow pump • Nonheparinized animals under anesthesia • Bleed via artery under anesthesia • Fixed pressure
	Control specified	not	Trauma	<ul style="list-style-type: none"> • Traumatic brain injury via weight drop • Rapid bleed with trauma via laparotomy during inhalational anesthesia • Trauma, not described, in nonheparinized animal
Other				<ul style="list-style-type: none"> • Blunt head trauma without hemorrhage • Renal ischemia (to produce hypovolemic anemia) under anesthesia • Shock induced intestinal ischemia via occluded superior mesenteric artery

(continued next page)

Table II-1 (continued)

Subject		Model		Variations
Large animal (pig, sheep, dog)	Hemorrhagic shock	Uncontrolled	Trauma	<ul style="list-style-type: none"> Liver avulsion and blunt chest trauma via captive bolt gun under anesthesia Liver crush injury and prolonged bleed Cerebral injury and prolonged bleed Femoral fracture and prolonged bleed
		No trauma		<ul style="list-style-type: none"> Lethal bleed via aortic tear Severe bleed via abdominal aorta in mechanically ventilated, anesthetized animals
		Controlled	Trauma	<ul style="list-style-type: none"> Controlled via artery with traumatic brain injury
			No Trauma	<ul style="list-style-type: none"> Controlled via jugular vein to simulate uncontrolled bleed with delayed (40 minutes) hypotensive resuscitation Controlled via artery in sedated, anesthetized animals breathing spontaneously Controlled, interrupted, in conscious animals
		Control specified	not trauma	<ul style="list-style-type: none"> Rapid bleed over 5 minutes followed by 2-minute cardiac arrest
	Other			<ul style="list-style-type: none"> Thrombocytopenia
Human studies	Hemorrhage	Uncontrolled	Trauma	<ul style="list-style-type: none"> Active bleed, multi-trauma critically ill (excludes traumatic brain injury) Penetrating torso wound Isolated traumatic brain injury Military combat
		No trauma		<ul style="list-style-type: none"> Acute bleed via esophageal varices
		Controlled	No trauma	<ul style="list-style-type: none"> Normal, healthy volunteers
	Other			<ul style="list-style-type: none"> Burn injury Elective surgery for abdominal aorta aneurysm

Other general response measures include:

- Microvascular integrity
- Type of surgical interventions required
- Cerebrovascular event or transient ischemic attack
- Neurological motor and behavioral functions

Outcome and efficacy measures include:

- Survival time; survival up to four weeks after injury for clinical studies

II.2.2 Cardiovascular stability

Six studies propose five types of treatment to support cardiovascular stability after hemorrhage. These studies employ both preclinical models and civilian and military patients in the pre-hospital setting and in trauma intensive care units.

II.2.2.1 Proposed treatments to promote cardiovascular stability

The preproposals include the following treatments:

1. Inhibition of myocardial stretch receptors by experimental agents as an adjunct to resuscitation fluid
2. Vasopressin and vasopressin analogues alone or in combination with diazoxide or Hextend®
3. Adrenomedullin and adrenomedullin-binding-protein-1 in combination with low volume resuscitation with lactated Ringer's solution
4. A novel agent, as an adjunct to resuscitation fluid, that blocks sodium and hydrogen exchange to decrease the amount of calcium entering cells in response to ischemia
5. Estrogen as an adjunct to conventional resuscitation fluid

II.2.2.2 Proposed measures of treatments that promote cardiovascular stability

In contrast to other proposed treatments, preproposals for studies to promote cardiovascular stability after hemorrhage did not propose to measure product characteristics.

Treatment-specific measures include:

- Pharmacokinetics (*i.e.*, plasma concentrations of treatment agent, metabolites and related compounds)
- Dose response
- Hemodynamic status (*e.g.*, blood pressure, heart rate)
- Assessment of cardiac function using echocardiography and other measures
- Loss of labeled albumin from intravascular spaces

Other general response measures include:

- Fluid requirements
- Bleeding times (from tail wound in preclinical studies)
- Urine output
- Early complications and adverse events
- Blood electrolyte concentrations
- Blood pH
- Blood and tissue oxygenation (*e.g.*, lactate concentrations, blood gases); microvascular tissue perfusion
- Body temperature
- Blood cultures
- Markers of cell stress and apoptosis; cytokine analysis of blood and organs
- Tissue edema, inflammation, and injury

- Markers of lung, liver, and kidney function; morphological changes in organs; histopathologic examination and tissue assays to assess end-organ function
- Mental status

Outcome and efficacy measures include:

- Duration of stay in intensive care unit
- Duration of hospitalization
- Survival

II.2.3 Oxygen delivery and/or reduction of ischemia

Thirteen studies proposed ten types of treatment to enhance oxygen delivery to the tissues after hemorrhage. Testing was proposed in preclinical models. The majority of treatments employ intravenous delivery and the remaining treatments are delivered via intramuscular or sublingual routes.

II.2.3.1 Proposed treatments to enhance oxygen delivery and/or limit ischemic damage

Treatments using hemoglobin-based oxygen carriers include:

1. Solutions containing polynitroxyl hemoglobin with and without TEMPOL that are used in combination with suspended animation
2. A proprietary colloidal solution containing hemoglobin conjugate and hydroxyethyl starch
3. Solution containing freeze-dried red blood cells and hydroxyethyl starch
4. Polyethylene glycol modified-hemoglobin, as powder and in lactated Ringer's-type solutions
5. Solution containing a liposome-encapsulated hemoglobin-based oxygen carrier
6. A patented solution containing hemoglobin that is cross-linked with ATP and adenosine
7. A hemoglobin-based oxygen carrier, tested with and without dehydroepiandrosterone (DHEA), androstenediol, and melatonin

Other treatments to enhance oxygen delivery and/or limit ischemic damage include:

8. Proprietary perfluorocarbon emulsions
9. Formulations of trans sodium crocetinate
10. Modified opioid

II.2.3.2 Proposed measures of treatments that enhance oxygen delivery and/or limit ischemic damage

Measures of product characteristics and development include:

- Measures to improve methods of manufacture
- Pyrogenicity
- Product solubility, stability, potency, and bioavailability

Treatment-specific measures include:

- Pharmacokinetics (*i.e.*, biodistribution and circulation half-life of experimental agent)
- Hemoglobin concentration; hemoglobin oxygen loading and binding capacity
- Blood and tissue oxygenation (*e.g.*, lactate concentrations)
- Oxidative tissue damage
- Dose response

Other general response measures include:

- Resuscitation fluid volume; minimal resuscitation fluid requirement
- Hemodynamic changes
- Acid-base status
- Antioxidant activity
- Inflammatory cytokine release/complement activation/inhibition (*e.g.*, plasma cytokines); RNA expression of stress protein
- Hypersensitivity reactions
- Cognitive function
- Toxicity

Outcome and efficacy measures include:

- Neural outcome (96-hr using two scoring systems and brain histology samples)
- Survival (10 day)

II.2.4 Cell structure and metabolism

Fourteen studies propose eleven types of treatment to support cell metabolism, integrity and repair after hemorrhage. Testing is proposed in preclinical models and in human civilian patients (type of Phase II study subjects not specified). The treatments are administered intravenously or intraperitoneally.

II.2.4.1 Proposed treatments to support cell metabolism, integrity (antioxidation) and cell repair

The preproposals include the following treatments:

1. Combination of polynitroxyl albumin and TEMPOL in normal saline, to be tested with and without induction of mild hypothermia
2. Combination of TEMPOL and other agents (*e.g.*, erythropoietin) in a hypertonic saline solution (7.5% NaCl)
3. Ethyl pyruvate with lactated Ringer's solution or hypertonic saline (7.5% NaCl) administered with or without other pharmacologic agents
4. Pyruvate with or without an agent to stabilize hypoxia-inducible factor-1 α and with or without an agent to suppress NAD(P)H oxidase activity added to a modified Krebs-Henseleit-type solution
5. Antioxidant vitamins in solution with β -hydroxybutyrate and fatty acids or in a hydroxyethylstarch colloid solution
6. D- β -hydroxybutyrate additive in a Ringer's-type solution

7. Lipid vesicles containing magnesium-ATP administered intravenously with or without resuscitation fluid or with commercial glucose-based peritoneal dialysis solution via the peritoneal cavity
8. An iron-binding drug attached to a modified starch and added in resuscitation fluids such as lactated Ringer's solution
9. Glucosamine as an adjunct to resuscitation fluid
10. An agent targeting peroxynitrite as an adjunct to resuscitation fluid
11. A compound of polyoxypropylene and polyoxyethylene as an additive in resuscitation fluid

II.2.4.2 Proposed measures of treatments supporting cell metabolism, integrity (antioxidation) and cell repair

Measures of product characteristics and development include:

- Product stability during storage and under varying environmental conditions simulating battlefield conditions

Treatment-specific measures include:

- Pharmacokinetics (*i.e.*, plasma, organ, and intracellular concentrations of treatment agent, metabolites, and related compounds)
- Markers of oxidation and antioxidant reserves (*e.g.*, blood oxyradicals)
- Oxygen consumption; change in the free energy of ATP hydrolysis
- Indices of apoptosis
- Determine optimal timing and dosage
- Determination of lethal dose (LD) for preclinical subjects (*i.e.*, LD₀, LD₅₀, LD₁₀₀)

Other general response measures include:

- Blood loss
- Plasma volume
- Hemodynamic status
- Blood coagulation profile
- Oxygen transport; blood and tissue oxygenation (*e.g.*, lactate concentrations, base deficit, blood gases); tissue perfusion
- Urine output
- Albumin loss from circulation; tissue edema
- Inflammatory response; cytokine analysis of blood and organs
- Immune parameters (*i.e.*, leukocyte and neutrophil infiltration, neutrophil function)
- Tissue adenine nucleotide concentration
- Nitric oxide and myeloperoxidase activity
- Markers of lung, heart, liver, and kidney function and injury; intestinal transit
- Neurological deficit scores
- Intestinal microcirculatory response; morphological change in jejunum (biopsy)
- Body weight of preclinical animal subjects
- Necropsy of animal subjects and histopathology after survival up to two weeks
- Toxicology

Outcome and efficacy measures include:

- Survival up to 24-hr and long-term

II.2.5 Inflammatory and immune responses

Six treatments are proposed to minimize inflammation and favorably modulate immune response after hemorrhage. Testing is proposed in preclinical models and in human civilian patients with acute esophageal variceal hemorrhage and for others with shock from penetrating torso injury. All treatments employ intravenous delivery.

II.2.5.1 Proposed treatments to minimize inflammation and favorably modulate immune response

The preproposals include the following treatments:

1. Infusion of reconstituted, lyophilized human recombinant interleukin-6 as an adjunct to resuscitation fluid
2. Cholinergic agonist additive in lactated Ringer's solution
3. Stearoyl additive in lactated Ringer's solution
4. A macrophage migration inhibitory factor additive in lactated Ringer's solution
5. A patented alpha-chemokine receptor inhibitor additive in lactated Ringer's solution
6. A proprietary combination drug therapy as an additive in resuscitation fluid

II.2.5.2 Proposed measures of treatments that minimize inflammation and favorably modulate immune response

Measures of product characteristics and development:

- Product stability studies

Treatment-specific measures:

- Pharmacokinetics (*i.e.*, plasma concentrations of treatment agent, metabolites and related compounds)
- Cytokine analysis of blood and organs; neutrophil activity
- Infection

Other general response measures:

- Fluid intake/requirement
- Urine output
- Hemodynamic status
- Arterial blood gases
- Microvascular tissue perfusion
- Tissue edema
- Assessment of liver, heart, kidney, and lung function or injury (*e.g.*, liver enzymes, pulmonary edema, adult respiratory distress syndrome, heart failure) Outcome and efficacy measures include:
- Survival

II.2.6 Miscellaneous strategies

Twelve studies proposed ten types of treatment that use miscellaneous fluids for volume expansion and for other purposes. Both preclinical models and testing in human civilian patients are proposed. The clinical studies would enroll patients with traumatic injuries in the pre-hospital and hospital setting or patients undergoing elective surgery for aneurysm of the abdominal aorta or other nonspecified subjects. Routes of fluid administration include oral, intravenous, intrathecal (intraspinal), and intraperitoneal.

II.2.6.1 Proposed miscellaneous treatments

The miscellaneous preproposals include the following treatments:

1. Small volume of hypertonic saline (7.5% NaCl)
2. Hypertonic saline with dextran (7.5% NaCl and 6% dextran-70)
3. Hextend® colloid solution
4. A proprietary hydroxyethyl starch colloid solution
5. Protein-supplemented lactated Ringer's solutions
6. A bicarbonated Ringer's solution
7. Oral rehydration solutions (*e.g.*, AstroAde, Gatorade®, and/or the oral rehydration solution advocated by the World Health Organization)
8. A commercial dialysis solution via peritoneal lavage as an adjunct to intravenous resuscitation fluids
9. Sterile water
10. A few proprietary blends of drugs currently marketed for other purposes as an adjunct to resuscitation fluid

II.2.6.2 Proposed measures of miscellaneous treatments

Measures of product characteristics and development include:

- Product formulation
- Validation of product sterilization and purity
- Testing the stability of experimental solutions under different environmental temperatures (*i.e.* after repeated freezing and thawing and other extreme shifts in storage temperatures simulating battlefield conditions)

Treatment-specific measures include:

- Pharmacokinetics (*i.e.*, biodistribution, circulation half-life, and clearance of experimental agent from circulation)
- Dose-response
- Volume of experimental fluid administered

Other general response measures include:

- Preclinical safety studies testing platelet function, irritation, sensitization, acute systemic toxicity, pyrogenicity, blood compatibility, disease transmission
- Fluid and blood requirements for the first 24-hours
- Plasma volume expansion
- Hemodynamic status (*e.g.*, blood pressure, heart rate, cardiac output)
- Urine output
- Assessment of edema
- Blood creatine kinase, lactate dehydrogenase
- Blood gases, blood pH, electrolyte and hematocrit concentrations
- Blood coagulation profile
- Blood and tissue oxygenation (*e.g.*, lactate concentrations) and total-body oxygen consumption
- Intracellular pH, ATP, phosphorus, and magnesium
- Cell viability and apoptosis
- Markers of inflammation and immune response (*e.g.*, cytokine production, neutrophil activation, gamma delta T cell function and signaling pathways)
- Septic complications
- Neuroendocrine response (*e.g.*, cortisol)

- Assay of vascular endothelial function
- Markers of organ function (*i.e.*, liver, lung, and kidney function, stomach emptying time; scores of end-organ function)
- Duration of mechanical ventilation

Outcome and efficacy measures include:

- Survival (*e.g.*, survival to discharge)

II.3 STRENGTHS AND LIMITATIONS OF SURVEY AND OTHER REMARKS

In surveying existing and developing resuscitation fluids and adjunct therapies, LSRO obtained numerous preproposals containing mostly diverse and sometimes complementary strategies.

II.3.1 Strengths of survey

More than twice the 25 to 30 submissions that the sponsor had anticipated were received. The preproposals represented broad categories of treatment strategies from international and U.S. researchers in academia, industry, and the military.

II.3.2 Limitations of survey

In hindsight, more detailed instructions to offerors in the request-for-information announcements would have provided offerors with more guidance both for determining the types of products/agents appropriate for submission and the inclusion of sufficient relevant information needed by the expert panel to review the preproposals.

Terminology used in the request-for-information announcements lacked specificity with respect to inclusion and exclusion criteria. Some offerors were confused as to what the product requirements were and what types of products would be included in the review (*i.e.*, resuscitation fluids) and excluded from review (*i.e.*, monitoring devices).

The request for novel resuscitation fluids lacked clear indication of the option to submit novel adjunct drugs that could be administered with one or more resuscitation fluids. In contrast, LSRO received several preproposals for the design of specific, defined formulations of a drug or agent in a specific resuscitation fluid vehicle (*e.g.*, augmented blood volume expander). The design of such defined-formulation products is in contrast to the more conventional approach of testing drug compatibility with various resuscitation fluids. For example, rather than testing the efficacy and compatibility of drug agent “X” with available resuscitations fluids, a specific formulation of drug agent “X” in a specific resuscitation fluid is proposed as one “product.”

The military relevance of resuscitation fluids can vary depending on whether a product is intended for use on the battlefield and/or must meet requirements of other echelons of care, such as use in a combat support hospital. All military product requirements for resuscitation fluid and adjunct therapies were not presented in the request-for-information announcements. Thus it may have been difficult for potential applicants to assess whether their product was militarily relevant. Moreover, one or more of the pre-conditions of therapy as specified in the announcement (hypotensive treatment) may have limited submissions of preproposals. In particular, potentially effective resuscitation fluids or adjunct therapies that can be administered independently of the listed pre-condition may not have been submitted.

Given the relatively short time between the announcements of the funding opportunity and the deadline for submission, some investigators of novel resuscitation fluid strategies currently under development may have

been unaware of the opportunity or lacked the time to respond. Therefore, the survey may be missing some novel approaches to resuscitation fluid.

II.3.3 Other remarks

LSRO is aware of other proposals for resuscitation fluid research that were not forwarded to the AFRRF expert panel for consideration.

II.3.3.1 Resuscitation Outcomes Consortium clinical trials on resuscitation fluids in civilian populations

In 2005, the Resuscitation Outcomes Consortium (ROC) planned to submit a R01 application to the National Institutes of Health for funding to conduct a clinical trial of resuscitation fluid. If funded, patient enrollment would begin in 2006. This proposed study involves a collaborative effort between three of the ROC sites (University of California San Diego, University of Washington, Seattle; and University of Toronto, Canada), along with the U.S. Army Institute of Surgical Research (San Antonio), and the University of Vermont. The researchers propose to study the inflammatory and coagulation response of patients to hypertonic resuscitation. Serial blood samples will be collected from patients over the first 24 hours after injury and samples will be analyzed for markers of the inflammatory response (*i.e.*, T cell, monocyte, and neutrophil activation) and for the coagulation response.

This effort is supportive of the larger ROC investigation in which two multi-center trials of hypertonic resuscitation will be conducted in two populations of trauma patients. In one study, blunt or penetrating trauma patients in hypovolemic shock will be enrolled to determine the impact of hypertonic resuscitation on survival. In the other study, blunt trauma patients with severe traumatic brain injury will be enrolled to determine the impact of hypertonic resuscitation on neurological outcome over a six month time period. Both studies will be three-arm, randomized, blinded intervention trials comparing hypertonic saline (7.5% NaCl), hypertonic saline with dextran (7.5% NaCl, 6% dextran 70), and normal saline as the initial resuscitation fluid administered in the pre-hospital setting (National Heart, Lung and Blood Institute, *et al.*, 2005).

The AFRRF expert panel did receive preproposals for clinical investigation of hypertonic saline and hypertonic saline with dextran from non-ROC investigators.

II.3.3.2 Defense Advanced Research Projects Agency interest in biological approaches to reduce morbidity and mortality from battlefield

The Defense Advanced Research Projects Agency (DARPA) posted a Broad Agency Announcement (BAA) on the Federal Funding Opportunities website to attract proposals for research on biological approaches to reduce morbidity and mortality from battlefield injury (DARPA, 2005). Specifically, DARPA received 23 proposals in response to addendum 3 of solicitation BAA04-12, “Surviving Blood Loss.”¹

Ten of these proposals investigate treatments comparable to preproposals forwarded to LSRO and for three of these the studies reviewed by LSRO had additional compounds extending the investigations.

Eight investigations of novel compounds proposed to DARPA were distinct from preproposals forwarded to LSRO. These investigations were in the discovery and early preclinical stages of product development. Studies were proposed to explore genomic and metabolic processes of hypometabolism and hibernation.

¹ One additional DARPA proposal was an extension of a proposal already submitted to DARPA by the same researcher.

Two additional proposals concerned the screening of a battery of compounds to identify agents of potential use for altered metabolic states. Another two proposals described the development of devices and one other proposal focused on the study of mechanisms of hibernation and did not propose to test pharmacologic agents.

II.3.3.3 Combat Casualty Care Research Programs in areas related to resuscitation fluids

LSRO is aware of the research effort of the Combat Casualty Care Research Programs to explore the potential therapeutic value of agents to influence the complement activation system (*e.g.*, C1q inhibitor and intravenous immunoglobulin). The goal of that effort is to identify complement activation inhibitors that could protect combat casualties from effects of shock as well as reduce the requirement for resuscitation fluid volume. LSRO did not specifically solicit preproposals on complement activation inhibitors, novel pharmaceuticals and biological agents that stop internal bleeding and/or that exert neuroprotective effects for traumatic brain injury. Therefore, the AFRRF survey might not have included such candidate therapies in the expert panel review and ranking.

III. MILITARY CONSIDERATIONS, REVIEW CRITERIA, AND LEADING CANDIDATES

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III. MILITARY CONSIDERATIONS, REVIEW CRITERIA, AND LEADING CANDIDATES

The preproposals submitted for consideration involve novel products and possibly precedent-setting methods or models. Such products, if later selected for development by the military, could potentially influence policy decisions and lead to changes in prevailing military practices. Therefore, the integrity of the process to develop review criteria and to select leading candidate products is important. Establishing review criteria and a rigorous and fair review process helps to ensure that the research selected by the sponsor for funding and product development has importance for the military's intended purpose, has scientific merit, and has sufficient quality.

This chapter specifies the criteria used to review preproposals and describes military considerations for product selection and development. The criteria and processing steps used by the expert panel are designed to apply to the review of future resuscitation fluid research proposals. The preliminary selection criteria include evaluations of the product's potential to improve resuscitation in combat injury situations. Improvements are characterized as increased survival, particularly during prolonged evacuation, with minimal morbidity.

III.1 OVERVIEW OF MILITARY PRODUCT DEVELOPMENT AND ADVANCEMENT OF LEADING CANDIDATES

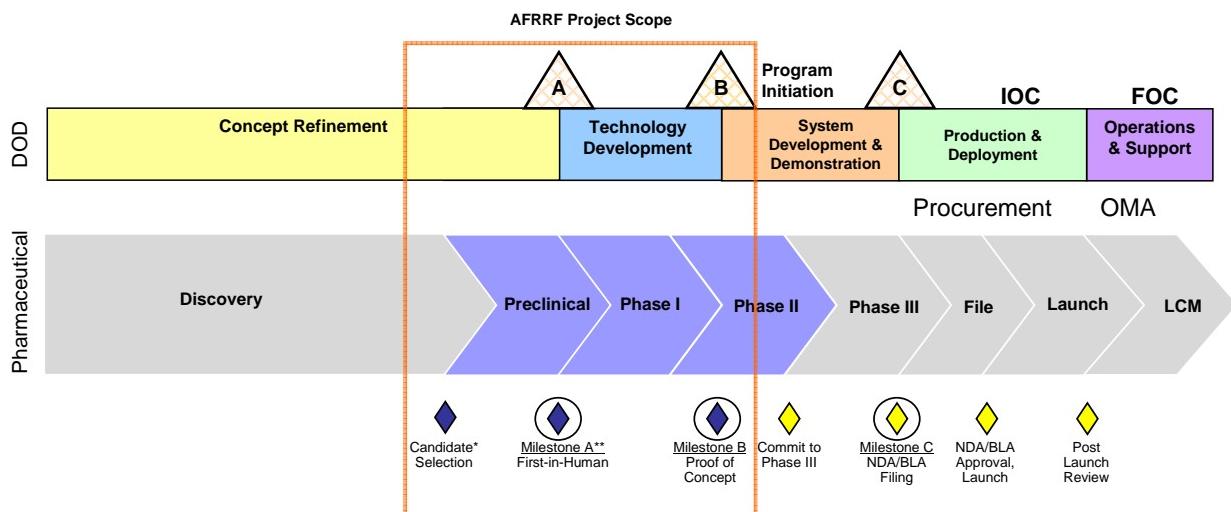
The military process for product development runs parallel to and is interconnected with the U.S. Food and Drug Administration's (FDA) product approval process, by which industry develops biomedical products. (See Figure III.1.) The sponsor established advancement criteria to assist in the identification of worthwhile products for development and to review products already in development. In selecting products for use in combat conditions, the military weighs short-term adverse effects against improved chances for survival.

III.1.1 Military milestones in product development

The military process of product development must be conducted fairly, using judicious decisions. This requires milestones for product development that are understandable to researchers and other stakeholders. Different data are needed at each stage of product development to reach these milestones.

Prior to testing a new treatment in humans, the product must undergo preclinical testing to address questions of safety and efficacy. Preclinical studies encompass *in vitro* and animal studies. Typically, standard *in vitro* analyses are used to characterize the identity, purity, strength, and composition of the product and its physiochemical properties. *In vitro* and small animal (*i.e.*, rodent) models can be helpful to investigate the mechanism of action. Small animal models are also used for testing potency, safety, and pharmacokinetics. Large animal models (*e.g.*, dogs, pigs, and sheep) are used to further assess the product's pharmacokinetics and pharmacodynamics and can provide supporting safety and efficacy data of the products.

The FDA evaluates preclinical evidence in order to grant investigational new drug (IND) status to a product. A product cannot proceed to a human clinical trial without obtaining IND status. When military-funded products reach the stage where IND status is deliberated, the military requires a pre-IND meeting with the FDA. After the pre-IND meeting and prior to preparing an IND application, the military determines whether to continue funding product development.



- * Entrance and advancement of a selected candidate is based on an agreed development plan and back-up strategy; multiple candidates enter at their respective stage of development and move through the development process.
- ** First-in-human decisions should occur after the FDA pre-IND meeting but prior to writing the IND application. If the first-in-human study is a small trial, milestone A may occur after positive results are obtained to understand if there is a potential solution to a known threat. In this situation, a meeting with the CG is still required.

Figure III.1 Working draft of the Department of Defense product development lifecycle. This sequence of events, which runs parallel to the FDA product approval process, is applied to drugs, vaccines, core programs, and congressional programs. A similar model is required for medical devices. AFRRF: Advanced first-responder resuscitation fluid; BLA: biologic license application; CG: Commanding General; DOD: Department of Defense; FDA: U.S. Food and Drug Administration; FOC: full operational capability; IND: investigational new drug; IOC: initial operational capability; LCM: Life Cycle Management; NDA: new drug application; OMA: operations and maintenance appropriation. Credit: Property of U.S. Army Medical Research and Materiel Command.

The military considers readiness for human studies to be the first milestone in product development. Human clinical IND trials are conducted in sequential order from Phase I through Phase III. The number and type of subjects studied differs with each development stage. Phase I trials typically test the safety of a new product in a small number of healthy human subjects and/or closely monitored patients. Tests are conducted to determine the safety, metabolism, pharmacologic action, immunogenicity, and other biologic effects of the treatment in humans.

Proof-of-concept is the second milestone in military product development and occurs during the Phase II stage of development. Phase II efficacy trials are designed to establish a safety profile and effective dose of the proposed agent in patients with the disease or condition under study. A Phase II study typically tests one dose or a small number of dosing ranges in patients and, when proof-of-concept is reached, proceeds to test in larger randomized, placebo-controlled studies of several dosing arms and/or comparative treatments. Phase II trials help identify common short-term side effects and risks in the target population. During this stage, evidence of safety and efficacy in humans is reviewed to provide sufficient confidence before the military invests in larger studies.

The third milestone in military product development is the filing of a new drug application. Phase III studies provide additional data on safety and efficacy under prescribed use conditions over long-term periods by enrolling larger numbers of patients. These studies are particularly helpful for identifying low-incidence adverse reactions. Based on the results of Phase III trials, a product may be approved by FDA for license and release in the market as a new drug. Subsequently, Phase IV trials can be conducted to provide additional safety data under conditions of actual usage by a broader spectrum of patients than had been previously studied in pre-market trials.

The scope of work for the Advanced First-Responder Resuscitation Fluid (AFRRF) project included products ranging from the preclinical stage of development through clinical Phase II. (See Figure III.1.) The product's stage of development influenced the type of review criteria imposed. The Life Sciences Research Office, Inc.

(LSRO) emphasizes, as discussed in Chapter I, that conducting clinical trials with a civilian population in a civilian environment is unlikely to adequately reflect the military conditions of use.

III.1.2 Military gatekeepers and advancement criteria

Positioning decision points at critical junctures in product development and assigning responsibility to gatekeeper committees and project teams ensures strategic evaluation of product viability, promotes cross-functional discussions on required product attributes and confirms that continued work efforts are aligned with the U.S. Army Medical Research and Materiel Command (USAMRMC) objectives.

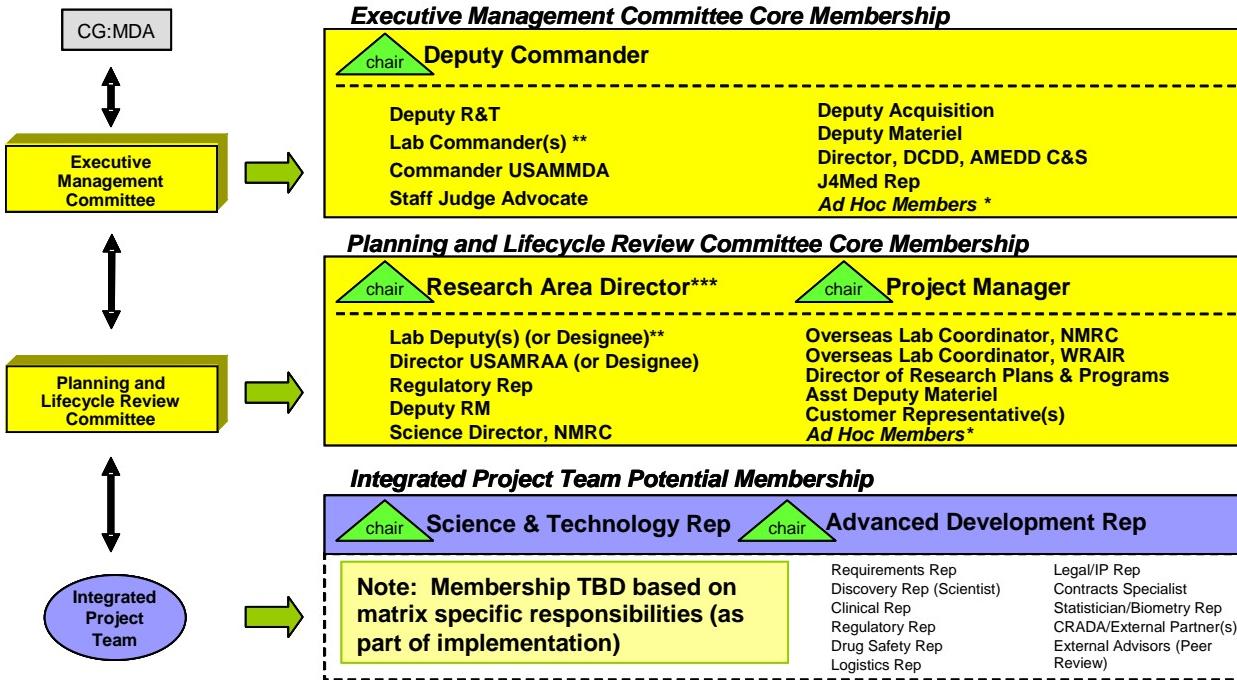
III.1.2.1 Gatekeeper committees and project team

In order for a product to receive initial funding or secure funding from the Department of Defense to advance between stages of development, it must gain approval in sequential order from the Integrated Project Team (IPT), the Planning and Lifecycle Review Committee, the Executive Management Committee, and in the case of clinical studies, from the Commanding General and Milestone Decision Authority. (See Figure III.2.) This process is currently under development and may undergo structural changes.

The IPT assesses and selects candidate products to forward to the Planning and Lifecycle Review Committee. The composition of the IPT is determined, in-part, by the responsibilities required for implementation of the product with consideration of its current stage of development.

The Planning and Lifecycle Review Committee analyzes the scientific and business feasibility of products forwarded by the IPT and determines whether or not to send a product to the Executive Management Committee. This committee is also responsible for planning and executing the development of specific products across the product lifecycle and maintaining communication between the IPT and the Executive Management Committee.

The Executive Management Committee evaluates how the product fits into the strategic alignment of military requirements and prioritizes the products advanced by the Planning and Lifecycle Review Committee. If a product is ready to be tested in preclinical studies, approval from the Executive Management Committee is sufficient to qualify the product as a leading candidate and funding for preclinical research can be issued. However, if a product is at the stage of advancing from the preclinical stage to Phase I, or advancing between clinical phases of development, the final approval for product advancement rests with the Commanding General and the Milestone Decisional Authority.



* Ad hoc members attend meetings by invitation and play an advisory role

** Representation from impacted laboratories are included when their respective products are being discussed

*** Planning and Lifecycle Review Committee will be chaired by Research Area Directors for products prior to milestone B (proof of concept); Project Managers chair committee for products from milestone B forward

Figure III.2 Diagram of communication lines between military gatekeepers in product development and membership roles. AMEDD C&S: Army Medical Department Center and School; CG: Commanding General; CRADA: Cooperative Research and Development Agreement; DCDD: Director of Combat and Doctrine Development; Deputy RM: Deputy Commander for Resource Management; Deputy R&T: Deputy Commander for Research and Technology; IP: Intellectual Property; J4Med Rep: Joint Chief of Staffs Logistics Directorate (J4) Medical Representative; MDA: Milestone Decision Authority; NMRC: Naval Medical Research Center; TBD: To be determined; USAMMDA: U.S. Army Medical Materiel Development Activity; USAMRAA: U.S. Army Medical Research Acquisition Activity; WRAIR: Walter Reed Army Institute of Research. Credit: Property of U.S. Army Medical Research and Materiel Command.

III.1.2.2 Military advancement criteria

To maintain a rigorous and consistent process for guiding product development, the military defines standard categories of advancement criteria for each major decision point of the product development lifecycle.

Advancement criteria are applied at the following decision points: (1) the point at which a product is selected for preclinical trials; (2) the advancement of a product to a Phase I human clinical trial; and (3) the progression of a product through proof-of-concept. Qualitative and quantitative requirements are identified within the standard categories of criteria for each decision point, to customize the criteria to individual products.

Advancement criteria provide a clearly defined and widely accessible understanding of product development requirements in each stage of development. These criteria enable the military to make objective decisions based on pre-defined product requirements and goals. Advancement criteria also impose scientific rigor and adequate business standards throughout the development lifecycle to increase the quality of products and programs and prevent late-stage product failures.

At the level of candidate selection, criteria address market feasibility, technical operations, safety, and efficacy. To advance to human testing, additional criteria are directed at intellectual property, stability and potency, labeling, and monitoring for adverse events. Further progression to proof-of-concept involves criteria that demonstrate human safety, effective dosing, and strategies for obtaining FDA approval.

III.1.3 Review considerations outlined by the sponsor

The following suggestions, as paraphrased here, were made by the sponsor for consideration by the expert panel. Although these points were considered, the expert panel did not necessarily agree with the sponsor or assign similar weight or priority as the sponsor for the purpose of its review.

The sponsor's considerations fall into five main categories: military relevance, scientific merit, process for product development, commercial viability, and current USAMRMC objectives and project management.

III.1.3.1 Military relevance

The sponsor will apply its own criteria for military relevance and other considerations to the leading candidates forwarded to them by the expert panel. However, the sponsor requested that the expert panel initially vet the candidates, to avoid substantial duplication of effort by the military.

The sponsor suggested the expert panel advance products that are designed for simplicity of safe use, remain stable and functional in a wide range of ambient temperature conditions, can be rapidly administered, and are of low volume/weight per unit dose to limit the burden of transport.

The sponsor indicated that there is a need for a product that works like whole blood without the typing and storage challenges. Therefore, the sponsor requested that the expert panel consider products that decrease the need for red blood cells. The sponsor specified the following desirable product characteristics:

- Will effectively stabilize patients with severe blood loss during extended evacuation delays for up to 72 hours
- Is well-suited for small volume resuscitation for trauma and blood loss (*i.e.*, can combine with hypotensive resuscitation)
- Has a specific indication for delivery, if it is an adjuvant therapy
- Adequately prevents/corrects coagulopathies

The ideal product will sustain wounded combatants, preserve organ function, achieve critical levels of blood pressure and tissue perfusion, and reduce mortality and late morbidity associated with trauma and serious blood loss. Current lines of investigation hint that this might be accomplished by reducing immune system activation and reducing oxygen radical generation during tissue re-oxygenation.

III.1.3.2 Scientific merit

The sponsor acknowledged the lack of a validated preclinical trauma model and did not expect the expert panel to debate this matter (Majde, 2003). However, the sponsor did underscore the need to utilize animal models of hemorrhagic shock in studying prolonged hypotensive resuscitation. Furthermore, the sponsor suggested that such studies include a non-anesthetized model to study hemorrhage alone, and an anesthetized model to study hemorrhage plus trauma. The sponsor cautioned the expert panel that having measures to describe the physiology of a product's mechanism is not sufficient, and that investigations must measure efficacy of improved survival in a relevant animal model. Safety is critical to FDA approval, thus the sponsor encouraged inclusion of preliminary safety data.

For clinical studies, the sponsor indicated the need for appropriate and clearly defined endpoints of survival. Such studies should have appropriate statistical power to achieve these endpoints. The sponsor suggested adding 2-3% more subjects to account for study effects in emergency departments and in field clinical trials. It is important to use enough subjects to discern significant differences in survival. Also, products that are being developed for surgical indications should be tested in a trauma population that reflects potential trauma in combat conditions.

AFRRF products will probably need to be tested in civilian head trauma patients. In combat emergency situations, the first-responder is typically unable to discern if the patient has head trauma. As discussed in section I.3.2.2, diminished cognition is used as a decision marker for the administration of AFRRF treatment in combat. Therefore, resuscitation fluids and adjunct therapies will likely be administered to some patients with head trauma.

Valid physiological endpoints of resuscitation are necessary to titrate the treatment appropriately and prevent fluid overload and additional stress on the heart.

The sponsor advocated providing as much control over treatment conditions as possible in clinical studies (*e.g.*, limiting the use of other products prior to the treatment and narrowing other confounding factors, such as heterogeneity of the subjects with respect to injury and past medical history.)

Products that increase survival will increase the numbers of sicker patients that live, so measures of morbidity following administration of these products are expected to demonstrate increased incidence.

III.1.3.3 Stage of product development

The sponsor instructed the expert panel to examine information about stage of development. If the product already has FDA approval for use in human trauma, surgery, or other uses, it is further along in its ability to be used for an alternate indication and/or under combat conditions. The sponsor noted that a product approved for intravenous administration would have to undergo a new FDA submission for another route (*e.g.*, intraosseous) which would require an indication for such a route.

III.1.3.4 Commercial viability

The depth of the military market is probably not sufficient to interest commercial manufacturers in producing products for exclusive use by the military. Therefore, the sponsor suggested that the expert panel consider the likelihood of the proposed product making it to, and remaining available in, the commercial marketplace. Products having a specific indication for pre-hospital resuscitation and/or other indications would drive FDA approval and increase market potential. A viable commercial market projection might encourage a manufacturer to allocate resources for product development and to obtain FDA approval.

III.1.3.5 USAMRMC objectives and project management

The sponsor sought four to eight leading AFRRF candidates and indicated that clinical studies were a high priority for funding.

The sponsor was interested in leading candidates with different therapeutic strategies (*e.g.*, one with oxygen-carrying capacity, one with anti-inflammatory benefits, one that delivers energy substrate to the cell) that might be able to obtain FDA approval independently. Several of these therapies may prove to be compatible and have positive added effects so that in the future, they might be combined in clinical trials.

The sponsor was also interested in leading candidates that would provide it with collaboration opportunities. Currently, the U.S. Army is collaborating with the National Heart Lung and Blood Institute to conduct human clinical trials through the Resuscitation Outcome Consortium (ROC) (*National Heart, Lung and Blood Institute, et al., 2005*). Part of the research identified by ROC as being within its target areas are:

- Evaluation of optimal strategies of fluid resuscitation including permissive hypotension, timing of initiation of infusion, and use of alternative fluids particularly after traumatic injury
- Use of immune modulators in improving clinical outcomes by altering systemic and/or regional inflammatory responses accompanying shock or shock-like states
- Evaluation of novel hemorrhage control strategies

The sponsor deploys a spiral process for product development, which accommodates staggered start dates for introducing new products into development. Sponsor representatives suggested that if the best candidates are four to five years away from clinical trial but the next best is ready now, then the sponsor might proceed with the candidate that is ready now and would consider implementing the other candidates later.

III.2 METHODS TO MINIMIZE POTENTIAL CONFLICT OF INTEREST

Conflict-of-interest and/or vested interest could bias the findings of the expert panel and unfairly alter the expert panel's findings and therefore must be avoided.

III.2.1 Life Sciences Research Office, Inc.

LSRO conducts review studies using procedures that place the utmost emphasis on minimizing bias and avoidance of vested interests.

III.2.1.1 Conflict-of-interest statements

In general, LSRO conflict-of-interest statements are analogous to requirements for Special Government Employees of the U.S. Government. (See Code of Federal Regulations, 73 CFR Subpart J, and FDA Staff Manual Guide 3118.2.) They specify actual or apparent conflict of interest, income, and investments, and reflect grants, contracts, consultancies, patents (issued or pending), and financial or other legal arrangements of the participant and of the participant's spouse, minor children, partner, and organization if they relate directly to the contractual activity.

For the purposes of this report, conflict-of-interest and vested interest refer to substantial personal participation in the study of novel resuscitation fluid and/or adjunct therapies by direct or indirect control of financial interests impacted by the nature of the study topic and/or the potential to benefit financially from policy decisions of the sponsor that result from the conclusions, recommendations, or suggestions of this LSRO expert panel.

LSRO staff members are required to complete such a conflict-of-interest statement upon employment, which is updated on an annual basis. Expert panel members in the AFRRF study completed a confidential statement of employment and financial interests. These conflict-of-interest statements were reviewed and signed by the LSRO Executive Director and reviewed by the LSRO Official Financial Representative.

III.2.1.2 Structured channels for communication

LSRO served as a conduit to relay information between the sponsor and the expert panel and between those submitting preproposals for consideration and the expert panel. In this way, potential bias that might be imposed on the expert panel by the sponsor and outside parties could be minimized. LSRO documented all related calls and other communications to and from LSRO.

III.2.2 Expert panel

To minimize potential conflict of interest, the expert panel planned a systematic process for reviewing and ranking preproposals. Expert panel members excused themselves from the meeting room during the review and ranking of preproposals if offerors (applicants) were from the member's institution/workplace, were individuals they have collaborated with during the past three years, or were individuals with whom they have or had a mentor relationship.

III.3 REVIEW PROTOCOL

The expert panel and LSRO adopted review criteria and applied evaluation methodology to select relevant studies of significant scientific merit from the pool of 59 preproposals included for consideration. (See section II.1.4.)

III.3.1 Preclinical and clinical groups

In general, the expert panel considered that preclinical studies could be better controlled and could have greater breadth of experimental procedures and measures than clinical studies yet may be more speculative than products ready for clinical trial. The expert panel categorized the submissions as preclinical or clinical depending on whether or not human test subjects were required. The expert panel did not further segregate preproposals by type of treatment (*i.e.*, blood volume expanders *vs.* drug or biologic agents *vs.* combination products) for purposes of ranking and prioritization.

Because the sponsor had indicated that clinical studies were a high priority for initial funding, the expert panel conducted a preliminary assessment of the clinical preproposals to identify missing information. Investigators were given 14 days to submit the information requested.

III.3.2 Review criteria

Review criteria emphasized military relevance, scientific merit, and quality. The expert panel attempted to balance the importance of military relevance and scientific merit when reviewing the preproposals.

III.3.2.1 Military relevance

The expert panel considered the military relevance of the preproposals in order to promote those candidate product/agents best suited to the sponsor's needs. The degree to which the preproposal met the military's intended purpose of increasing survival and reducing morbidity in extended evacuation situations was considered as a component of military relevance. Military relevance was based on the likelihood that:

- The proposed approach could be applied by first-responders on a battlefield
- The treatment might substantially improve survival from exsanguinating shock, either during prolonged evacuation or via its impact on long-term survival (Products administered by first-responders that were effective in reducing the risk of later complications, such as sepsis and organ failure, served as an example of products that might improve long-term survival.)

Moreover, "fatal flaws" for military use, such as product instability under battlefield conditions, influenced the score for military relevance.

III.3.2.2 Scientific merit

Drawing upon scientific criteria utilized by the National Institutes of Health (2005), the major considerations of scientific merit were:

- Significance – the potential for advancing scientific knowledge and clinical practice of treating hemorrhage with resuscitation fluid in combat
- Approach – appropriateness of research design for proposed application
- Innovation – originality of concept, product and/or methods
- Investigators and environment – experience of investigators with proposed treatment and scientific capabilities of experimental setting

The following were also considered:

- Preliminary supporting data
- Whether the aims of the project were appropriate for the product's current stage of development.
- Feasibility of proposed treatment and experimental trials
- Product safety and potential for obtaining community consent for pre-hospital clinical studies ("community consent" indicates approval by representatives of the community charged with evaluating product safety data.)

III.3.3 Scoring and ranking

Preproposals were scored and ranked so that the sponsor could identify strategies that have the greatest potential to save lives on the battlefield and reduce later morbidity and mortality. Those that did not meet minimum standards of evidence were eliminated from further consideration.

Military relevance was scored on a scale of one to five, with the score of one being the best score possible. Similarly, scientific merit was scored on a scale of one to five, with one as the best score possible.

III.3.3.1 Initial scoring by lead reviewers

Due to the great number of preproposals received for review, two lead reviewers conducted initial reviews so that preproposals of insufficient military relevance and/or scientific merit could be eliminated.

Expert panel members were assigned to preproposals within their area of expertise and research interests, provided reviewers were free from potential conflicts of interest. Multiple pairs of lead reviewers were formed so that each panel member was paired with at least two others. Lead reviewers each read 15 to 18 preproposals thoroughly over six weeks.

The expert panel members designed a form to assist with systematic application of review criteria. (Figure III.3.) It prompts the reviewer to:

- Categorize the study as preclinical or clinical
- Summarize the research plan
- Note any issues related to the potential commercial appeal of the product
- Score the military relevance of the proposed product on a scale of one (excellent) to five (poor)
- Score the scientific merit of the proposed product on a scale of one (excellent) to five (poor)
- Identify strengths and weaknesses

Lead reviewers scored preproposals independently. The expert panel members submitted their completed review forms to LSRO staff, who compiled the initial scores and comments for presentation to the entire panel.

Critique form for initial review of preproposals and proposals of advanced-first responder resuscitation fluids and adjunct therapies

Group (preclinical or clinical):

Assigned identification number of preproposal/proposal:

Title of project:

Principal applicant (Offeror):

Institution:

Description – (Four-sentence maximum. Provide a brief description of project, including the hypothesis, main methods and primary data to be collected.)

Critique

Commercial Appeal

Note any remarkable commercial considerations of treatment/product, such as:

- Market volume in non-war environment, *i.e.*, dual use and use in civilian environment
- Profit margin
- Manufacturer's scale of production; Good Manufacturing Practice conditions
- Regulatory/FDA considerations; will proposed treatment be approved for some indication?
- Is it likely to be available?

Comments only (not scored):

Military Relevance [One Score, 1 (excellent) to 5 (poor)]

Consider the following:

- What is the likelihood that this approach could be applied by first-responders on a battlefield?
- Does this approach increase the probability of improving survival from exsanguinating shock?
- Are there “fatal flaws” for military use, such as product instability, short shelf-life, incompatibility with use in austere environment, unsatisfactory route of administration, high volume/weight, storage and transport limitations, overwhelming technical difficulties, unsafe for use on front lines.

Military Relevance Score: _____

SCIENTIFIC MERIT [ONE SCORE, 1 (EXCELLENT) TO 5 (POOR)]

Consider the following:

- **Significance.** Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice advance? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?
- **Approach.** Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics? Consider the (a) safety given “community consent” issues; (b) preliminary data; (c) feasibility of the treatment and trial/study.
- **Innovation.** Is the project original and innovative? For example: does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?
- **Investigators and Environment.** Investigators: Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project? Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

Scientific Merit Score: _____

Summary – (Four-sentence maximum. Provide a brief description of strengths and weaknesses of the preproposal/proposal)

Date of Review:

Reviewer:

Figure III.3 Critique form for initial review of preproposals and proposals. This form was modified from reviewer guidelines used by the National Institutes of Health [<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-002.html>]. FDA: U.S. Food and Drug Administration.

III.3.3.2 Elimination of preproposals lacking sufficient military relevance and/or scientific merit

During an expert panel meeting, the lead reviewers guided discussion of the merits and limitations of each preproposal. Where there was a large discrepancy in scores between lead reviewers (e.g., score of one for military relevance by one lead reviewer and a score of five by the second) the expert panel was particularly keen to understand the basis for the difference. After discussion by the expert panel, the lead reviewers were given an opportunity to modify their initial scores and verbally stated these to the expert panel.

The expert panel considered preproposals scoring a three or higher for military relevance from both lead reviewers to have insufficient relevance. For scientific merit, preproposals scoring a three or higher from one reviewer and a four or higher from the second reviewer were considered of insufficient scientific merit. Table III-1 illustrates how scoring could impact a preproposal's advancement to the next round of scoring.

Table III-1 Example of lead reviewer scoring of military relevance and scientific merit. Lead reviewers could affect advancement of preproposals to the next round of scoring. Scores are on a scale of one (excellent) to five (poor).

Preproposal	Reviewer-1 Scores		Reviewer-2 Scores		Comments
	Military	Scientific	Military	Scientific	
W	2.0	4.0	3.0	3.0	Insufficient scientific merit
X	3.0	1.0	3.0	2.5	Insufficient military relevance
Y	1.0	1.0	2.0	2.0	Advances to full panel scoring
Z	1.5	2.0	1.0	3.0	Advances to full panel scoring

III.3.3.3 Final scores and ranking

The expert panel advanced and re-scored those preproposals that had received sufficient scores from lead reviewers for both military relevance and scientific merit.

In the second round of scoring, each expert panel member privately evaluated scientific merit and military relevance. Although lead reviewers had previously verbally stated any modified first-round scores to the expert panel, they were able to change their scores without verbal notice during private second-round scoring by the full panel.

The score sheets were collected from individual panel members by LSRO staff, which entered scores into Microsoft® Excel spreadsheets. Three aggregate scores were calculated for each preproposal: (1) the average score for military relevance, (2) the average score for scientific merit, and (3) a total overall score, calculated as the sum of (1) and (2). (An example of scoring by the full panel is presented in Table III-2.)

Within clinical and preclinical groups, the rank-order of preproposals was determined for each of the three categories of scoring as stated above. For the purpose of selecting leading candidates, preproposals were rank-ordered by the total overall score, from lowest (excellent) to highest (poor) score. Ranking was based on individual scoring and comparisons were not made between the preproposals to alter ranking.

Table III-2 Example of full panel scoring of military relevance and scientific merit. Scores are on a scale of one (excellent) to five (poor). In this example, preproposal “Z” has the best total score overall.

Panel Member	Preproposal Y		Preproposal Z	
	Military	Scientific	Military	Scientific
1	2.0	2.0	1.0	2.0
2	1.0	1.5	1.0	2.0
3	3.0	2.0	1.0	2.0
4	*	*	2.0	2.0
5	2.0	2.0	2.0	3.0
6	1.5	2.0	1.0	2.0
7	2.0	2.0	1.0	2.5
Average	1.9	1.9	1.3	2.2
Total Sum Score (sum of two averages)	3.8		3.5	

*Panel member absent from discussion and scoring because of potential conflict of interest.

Preclinical preproposals were further subdivided into top (leading candidates), middle, and minor tiers based on rank-order in all three aggregate scores. Leading candidates had the best overall scores for both scientific merit and military relevance, ranking in single digits (first to ninth place). Middle-tier candidates rank below leading candidates in overall score and ranked in double-digits (10th place or worse) for at least one of the three aggregate scores. Minor-tier candidates ranked in double-digits for all three categories of scoring and had the poorest overall scores. Table III-3 presents an example of ranking.

III.3.4 Characterization of ranked products

III.3.4.1 Type of treatment and stage of product development

The products under consideration were categorized by one or more general descriptions of their hypothesized mode of action:

- Anti-inflammatory
- Antioxidant
- Non-specific cytoprotector
- Augmented blood volume expander
- Hemoglobin-based oxygen carrier
- Oxygen transport facilitator
- Other

Table III-3 Example of ranking of preproposals using total sum scores for military relevance and scientific merit. In this example, preproposal “Z” has the best total score overall and ranks highest on a scale of one (excellent) to five (poor).

Preproposal	Military	Score Scientific	Total Sum Score	Rank		Total Sum Score
				Military	Scientific	
Z	1.3	2.2	3.5	1	2	1
Y	1.9	1.9	3.8	2	1	2

The stage of product development was categorized leniently, assuming the best progress possible, as one of the following:

- Discovery (not yet tested in animals, an estimated 7 or more years from human clinical trial)
- Early preclinical (an estimated 5 to 6 years from human clinical trial)
- Mid-preclinical (safety testing, an estimated 3 to 4 years from human clinical trial)
- Late preclinical (testing in relevant animal model, an estimated 1 to 2 years from human clinical trial)
- Clinical Phase I
- Clinical Phase II
- Clinical Phase III

- Clinical Phase IV

III.3.4.2 Potential for commercial viability

The sponsor emphasized that the military demand for resuscitation fluid fluctuates depending on whether or not the military is engaged in war, and that a commercial partner would likely be needed to share development costs. Therefore, resuscitation fluid products with dual use in both the military and civilian markets were preferred.

The expert panel estimated whether each ranked product would be commercially successful outside the military environment. The commercial aspects considered included indications for use in civilian populations, protection of intellectual property (*i.e.*, patent protection), existing FDA approval for some other use, potential profitability, and the feasibility of production based on the type and availability of product components. Assuming a product performed as hypothesized, its non-military market potential was rated leniently as having (a) high, (b) medium, or (c) low commercial appeal.

III.3.5 Strengths and limitations of the review process

III.3.5.1 Strengths

Expert panel members were knowledgeable and experienced in critical care, trauma surgery, anesthesiology, clinical pharmacology, resuscitation fluid product development, and resuscitation science research in animals and humans, with subspecialties in shock research, cardiovascular disorders, neurotrauma, and thermal injuries. The number of expert panel members was sufficient to cover the work-load and provide depth of perspective, even when individual expert panel members excused themselves from discussion because of potential conflicts of interest. Expert panel members also benefited from sharing knowledge and viewpoints prior to finalizing their review decisions.

III.3.5.2 Limitations

Although some members of the expert panel had served in the armed forces, the expert panel lacked specific expertise in the use of resuscitation fluid by battlefield first-responders and relied on information provided by the sponsor for use in the assessment of military relevance. LSRO arranged for sponsor representatives who were knowledgeable in the use of resuscitation fluid by first responders to be available to answer questions from the expert panel during the course of the review. However, the expert panel did not ask questions of these representatives.

The expert panel acknowledged the difficulty of comparing preproposals in different stages of product development, in that proposed treatments ranged from the discovery stage through to Phase II human clinical trials. Furthermore, it recognized the difficulty of comparing preproposals with very different strategies for resuscitation fluid therapy. As a result, preproposals were not evaluated relative to one another, but ranked by scoring their individual merits and limitations using standardized criteria.

Military relevance was difficult to assess for products lacking specific formulation information. Many preproposals lacked relevant information and sufficient detail for definitive evaluations. Therefore, full proposals might score and rank differently than their respective preproposals, even if similar review criteria are applied. For similar reasons, differences up to one point in rank order of preproposals may not be relevant for funding decisions.

III.4 CANDIDATE TECHNOLOGIES

The expert panel evaluated 59 preproposals in accordance with the rules set forth for review criteria. This resulted in identification of leading candidates meriting further review of a detailed full proposal.

Panel deliberations involved an exchange of ideas and evaluations of the attributes of the preproposals. LSRO staff prepared critiques of each of the 59 preproposals using the brief summaries from the initial review forms of the two lead reviewers supplemented with comments of the expert panel. The critiques were intended to summarize discussions and may have omitted minor strengths and weaknesses.

III.4.1 Preproposals eliminated as insufficient for funding

Lead reviewers scored some preproposals so poorly on military relevance and/or scientific merit that they were categorized as “insufficient for funding” and were eliminated from further review. Several preproposals lacked minimal required data, which impeded evaluations and contributed to poor scores. Products that are relevant or can be modified to be relevant, but whose corresponding preproposals were evaluated as insufficient, represent a pool of potential products for future development if new preproposals for these products offer sufficient scientific merit.

Of ten clinical preproposals considered, eight (80% of total clinical) were excluded from scoring by the full panel: four (50%) for insufficient military relevance (scores of 3.0 or higher from both lead reviewers), three (37.5%) for insufficient scientific merit (score of 3.0 or higher from one lead reviewer and score of 4.0 or higher from the second lead reviewer) and one (12.5%) for insufficient military relevance and scientific merit (Figure III.4).

Of 49 preclinical preproposals considered, 27 (55% of total preclinical) did not advance to scoring by the full expert panel: five (18.5%) for insufficient military relevance, nine (33%) for insufficient scientific merit and thirteen (48%) for insufficient military relevance and scientific merit. (See Figure III.4.)

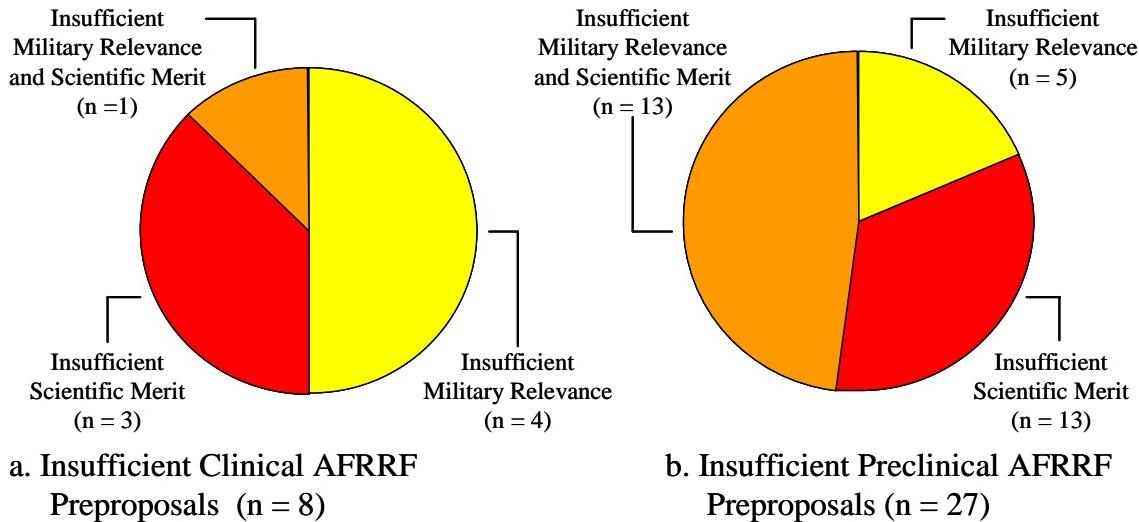


Figure III.4 Insufficient preproposals.

III.4.2 Ranked preproposals

After elimination of 35 insufficient preproposals, the remaining 24 were ranked. The expert panel identified two leading clinical preproposals. One is an FDA-approved agent for use in surgery. The other is an agent that is progressing to Phase II clinical trials, the commercial viability of which, if the agent proves to be an effective therapy, was estimated to be moderate.

Twenty-two preclinical preproposals were grouped into three tiers: (1) five preclinical preproposals in the top tier (best total scores), (2) nine in the middle tier, and (3) eight in the minor tier. The preclinical candidate with the best total score also had the best scores for both military relevance and scientific merit. The remaining four top-tier preclinical candidates for total score also ranked eighth place or better for both military relevance and scientific merit.

One of the two leading clinical preproposals had an average score of 3.29 for military relevance, a value considered borderline-sufficient by the expert panel. The lowest ranked preclinical preproposal had borderline-sufficient average scores of 3.50 and 3.57 for military relevance and scientific merit, respectively. (See Figure III.5.) All preclinical preproposals in the top tier had better scores for scientific merit than the two leading clinical preproposals. Furthermore, all preclinical preproposals in the top and middle tiers had better scores for military relevance than the two leading clinical preproposals.

The 24 ranked preproposals include resuscitation fluids as well as adjuncts to resuscitation fluid. The expert panel categorized ranked preproposals by their AFRRF treatment: anti-inflammatory, augmented blood volume expander, cytoprotector, hemoglobin-based oxygen carrier, oxygen transport facilitator, or an agent that influenced coagulation (coagulation effector). Some therapies spanned more than one category of treatment, and are represented in Figure III.6 as combination treatments. Several preproposals of anti-inflammatory treatments rated highly. Specifically, one of the two leading clinical preproposals and seven of the top ten preclinical preproposals included anti-inflammatory therapies.

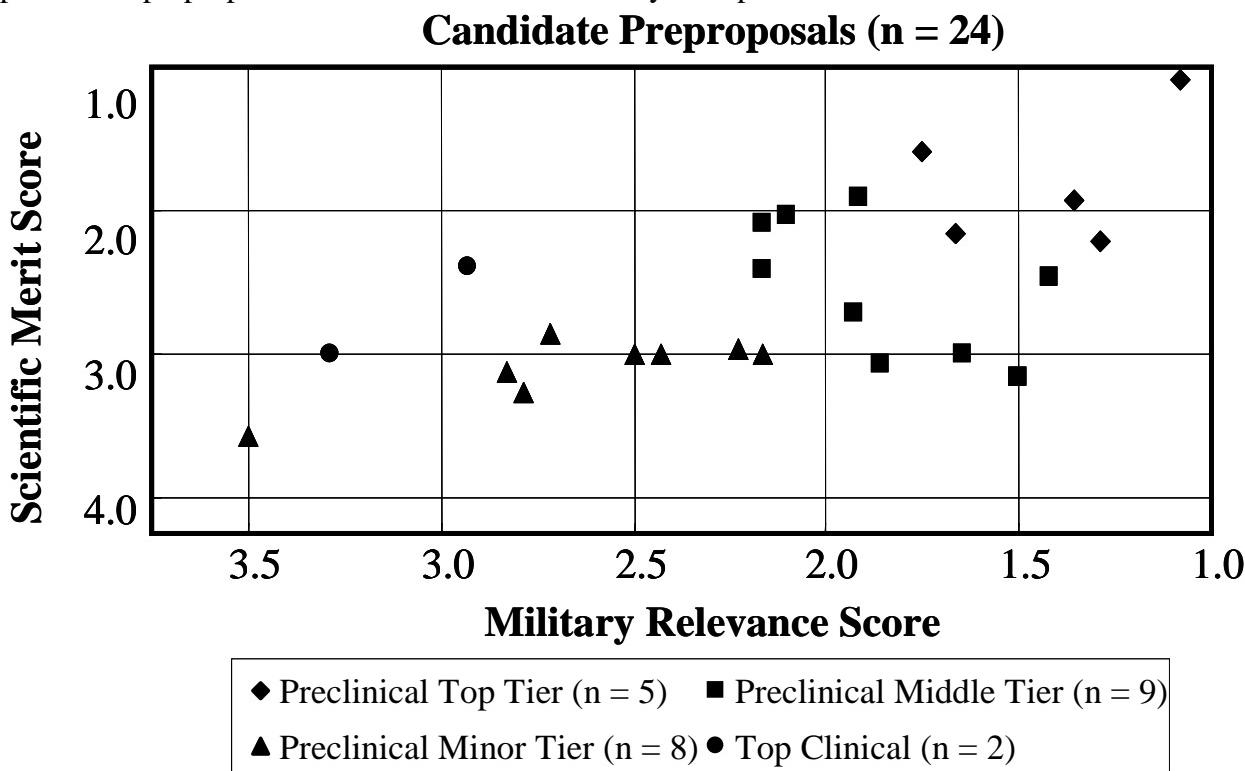


Figure III.5 Scores assigned to preproposals by the expert panel. The lower the numerical score, the better the ranking. Not shown: scores for 35 preproposals eliminated for insufficient military relevance and/or scientific merit.

Both leading clinical preproposals indicated time periods for funding; one requested funding for a five-year period to include 3.5 years of subject recruitment and data collection, and the other proposed a project that included several trials, one of which could be conducted in one or two years by the estimate of the investigator. Only five of the top 14 preclinical preproposals specified a duration of funding, which ranged from one year to

three years. Several offerors divided their project into two or more aims that were each assigned a timetable for completion (*i.e.*, first aim: 1.5 years; second aim: additional 1.5 years).

The top two preclinical candidates were estimated to be, at best, within four years of human clinical trials; the remaining three candidates in the top tier were estimated to be five or more years from human clinical trials. One product, an augmented blood volume expander, is at best two years from clinical trials; its total score ranked sixth among preclinical preproposals.

III.5 SUMMARY

Military gatekeeper committees and project teams select products for funding and ensure strategic evaluation of product viability during research and development. In addition, the military relies on the advice of independent experts for peer-review of preproposals and proposals to assist it in the selection of projects for funding. For the AFRRF project, the sponsor indicated that clinical studies were a high priority for funding and asked the expert panel to identify four to eight leading clinical and/or preclinical candidates.

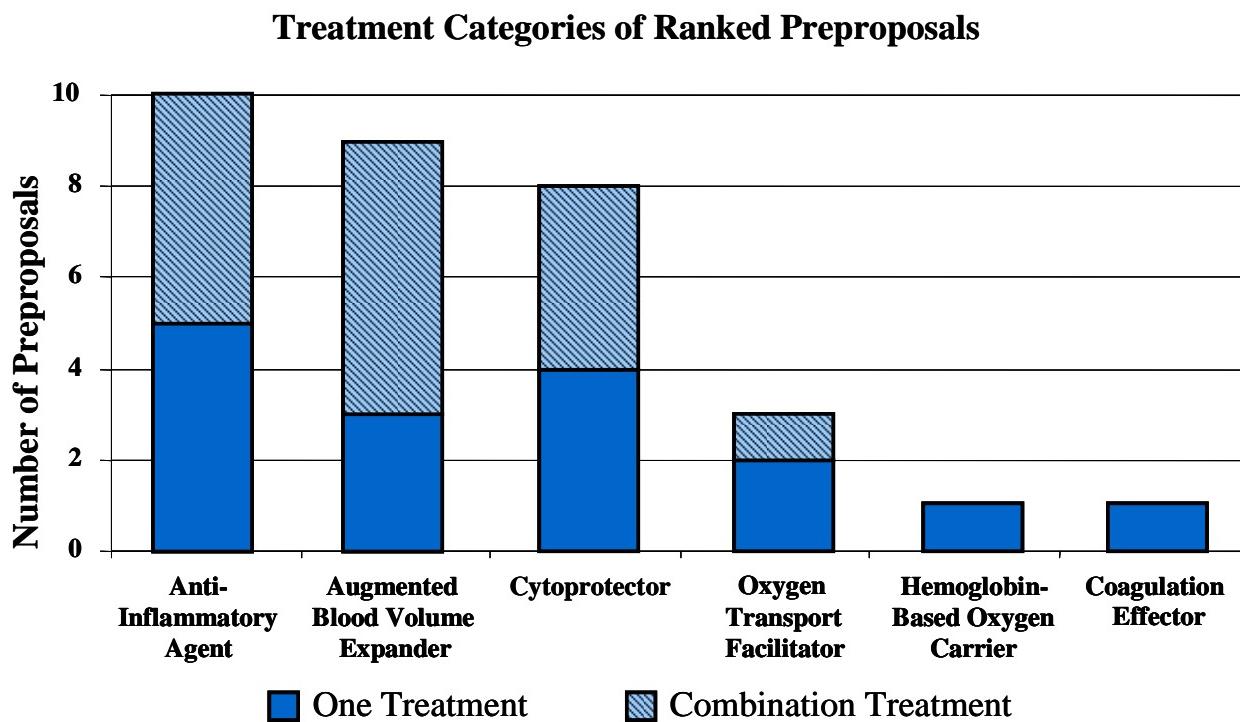


Figure III.6 Twenty-four ranked preproposals categorized by their proposed treatment. Some treatments spanned more than one category, represented here as combination treatments.

The expert panel selected review criteria and developed an initial review form, which it applied to the 59 preproposals under consideration. In addition to scientific merit, review included an assessment of military relevance based on the likelihood that the proposed approach could be applied by first-responders on a battlefield and whether the treatment might substantially improve survival from exsanguinating hemorrhage, either during prolonged evacuation or via its impact on long-term survival.

Two leading clinical AFRRF candidates were identified. Five leading preclinical preproposals were identified that had better scores for military relevance and scientific merit than the clinical preproposals. The preclinical candidate with the best total score also ranked first for both military relevance and scientific merit.

For the two leading clinical candidates, one is already approved by FDA for use in surgery and the other agent, should it prove to be an effective therapy, was estimated to be moderately viable in the commercial market. Assuming the products perform as hypothesized, the non-military market potential for the three leading preclinical products was rated highly. The remaining two preclinical candidates in the top tier were assessed as having moderate commercial appeal.

Several preproposals of anti-inflammatory treatments rated highly. One of the two leading clinical preproposals and seven of the top ten preclinical preproposals included anti-inflammatory therapies.

IV. FRAMEWORK FOR SCIENTIFIC REVIEWS OF PROPOSED RESEARCH FOR RESUSCITATION FLUIDS AND ADJUNCT THERAPIES

IV.1 RECOMMENDED FRAMEWORK FOR FUTURE SCIENTIFIC REVIEWS

- IV.1.1 Framing the research program
 - IV.1.1.1 Research program duration
 - IV.1.1.2 Standing committee and review panels
 - IV.1.1.3 Proposed funding cycles and progress monitoring
- IV.1.2 Framing the categories of therapy
 - IV.1.2.1 Novel blood volume expanders, pharmacologic agents, and combination products
 - IV.1.2.2 Indications and product requirements for military relevance
- IV.1.3 Framing the relevant experimental models
 - IV.1.3.1 Recommendations for preclinical studies
 - IV.1.3.2 Recommendations for human studies
- IV.1.4 Further research to advance resuscitation science and improve survival from combat injuries
 - IV.1.4.1 Framing basic questions
 - IV.1.4.2 Framing the environment for resuscitative care

IV.2 RECOMMENDED PROCESSES AND FORMS FOR PROPOSALS

- IV.2.1 Recommendations for future preproposals
- IV.2.2 Specified format and content areas
 - IV.2.2.1 Recommendations and the current USAMRMC format
 - IV.2.2.2 Identification and characterization of the product/agent
 - IV.2.2.3 Military relevance of product/agent
 - IV.2.2.4 Protection of human subjects
 - IV.2.2.5 Justification of the proposed animal model
 - IV.2.2.6 Additional format considerations
- IV.2.3 Public announcements and other communications
 - IV.2.3.1 Guidance for future Broad Agency Announcements
 - IV.2.3.2 Website for AFRRF research
 - IV.2.3.3 Database of interested parties
 - IV.2.3.4 Point-of-contact experts and other communications

IV.3 RECOMMENDATIONS FOR FUTURE PEER REVIEW

- IV.3.1 Expert panel
- IV.3.2 Preparation for review
- IV.3.3 Review criteria for preproposals and proposals
- IV.3.4 Leading candidates

IV.4 SUMMARY

- IV.4.1 Recommendations for the framework for reviewing proposals
- IV.4.2 Recommendations for future proposal processes and forms
- IV.4.3 Recommendations for experimental models and clinical studies

IV. FRAMEWORK FOR SCIENTIFIC REVIEWS OF PROPOSED RESEARCH FOR RESUSCITATION FLUIDS AND ADJUNCT THERAPIES

In this chapter, the Life Sciences Research Office, Inc. (LSRO) and the expert panel suggest a framework for future scientific reviews of proposed advanced first-responder resuscitation fluid (AFRRF) research. To improve the military relevance, scientific merit, and quality of future grant proposals, specific format recommendations and minimum data requirements for preproposal and proposal submissions are made.

IV.1 RECOMMENDED FRAMEWORK FOR FUTURE SCIENTIFIC REVIEWS

The expert panel identified several aspects of the Combat Casualty Care Research Program (CCCRP) where expert panel guidance might improve future scientific reviews and prioritization of AFRRF research. The expert panel considered projected timeframes for product development, the expertise and organization of participants in the peer-review process, categories of novel therapies with the potential to substantially improve survival from hemorrhagic shock on the battlefield, relevant experimental models, and areas for future resuscitation science research.

IV.1.1 Framing the research program

The expert panel discussed several aspects of CCCR P that are structured to support development of an AFRRF product. The expert panel considered the time frame of a programmatic commitment to AFRRF, the possible organization of a standing committee for periodic peer-review, the duration of funding for specific proposals, and the necessity of monitoring the progress of funded proposals.

IV.1.1.1 Research program duration

Neither the National Institutes of Health (NIH) nor other federal programs outside the military are obligated to advance the research and practice of medicine unique to combat medicine. Therefore, LSRO and the expert panel considered it imperative that CCCR P and the corresponding program at the Office of Naval Research (ONR) continue to support these critical functions.

Once a product reaches the clinical trial phase of development, the effort to hire staff and build the infrastructure to support and conduct progressive trials will likely take longer than six years. Based on the preproposals that were submitted, the expert panel considered it unlikely that a new AFRRF product would be ready for military use by 2011. Therefore, the expert panel determined that the development of a novel AFRRF product would require funding support that extends beyond 2011. Moreover, a longer-term commitment by the U.S. Army Medical Research and Materiel Command (USAMRMC) would ensure that CCCR P would be able to retain staff members who are knowledgeable about AFRRF research and product development and recruit additional AFRRF experts as such positions become available.

IV.1.1.2 Standing committee and review panels

The expert panel recommended that the sponsor create a multidisciplinary standing committee of experts. The committee would review the military relevance, scientific merit, and commercial viability of future preproposals. The disciplines represented in the standing committee should resemble those of the current expert panel (listed in section III.3.5.1). Rather than having a military expert member on the standing committee, the military should assign one or two military experts as consultants to the standing committee. Such military experts would read all preproposals or proposals and verify that the expert panel's interpretation of the military relevance of the product/agent was accurate, but would not participate in the review of scientific merit, scoring, or ranking.

The expert panel recommended that the sponsor obtain input from the standing committee when preparing future invitations and announcements for preproposals or proposals for AFRRF awards. The committee would confirm that requests for information are consistent with the criteria for evaluation.

The expert panel suggested that the sponsor create a website or other mechanism to accept preproposals on a continuous basis or by scheduled deadlines, and advised the sponsor to forward preproposals electronically to the standing committee for review on a quarterly basis.

Members of the standing committee would prepare critiques of the preproposals and score them on military relevance and scientific merit as outlined by the AFRRF expert panel. Commercial viability would also be considered within the critique. A conference call of the standing committee members could be organized, if required, to finalize preproposal scores for ranking purposes. The standing committee would provide continuity over time and be able to identify previously evaluated ideas. The standing committee would identify leading candidates for the sponsor.

While a multidisciplinary standing committee would ensure broad expertise, some preproposals might require additional content expertise not available to the committee. Should a preproposal be identified to require expertise not available to the standing committee, *ad hoc* reviewers should be identified and brought in to the review process.

The volume of preproposals and proposals might make a single standing committee undesirable. A mechanism may be needed to expand the capacity of the standing committee to provide timely reviews. One option might be to have all preproposals reviewed by the standing committee and periodically assemble review panels for full proposals. Individual review panels would include members of the standing committee as well as *ad hoc* reviewers. The composition of the review panel might be tailored to the type of proposals being reviewed.

The expert panel recommended that the obligations of the proposed standing committee and review panels mimic respective mechanisms used by NIH, such as scheduling annual meeting dates for the purpose of reviewing proposals. Deadlines for the proposals would need to be coordinated with the annual meeting of the standing committee or review panel. The expert panel also valued the role of an independent intermediary (*e.g.*, LSRO) to act as an interface between the sponsor and the standing committee and provide staff support to the standing committee and review panels.

IV.1.1.3 Proposed funding cycles and progress monitoring

The expert panel encouraged the sponsor to fund specific proposals for limited cycles, subject funded projects to periodic evaluations, and employ competitive processes for previously funded offerors (applicants) to obtain funding for new proposals. The expert panel determined that a budget cycle of two years maximum would be adequate for preclinical studies to test hypotheses and demonstrate the results necessary for product advancement. Since clinical studies are more complex and time intensive, the expert panel recommended the budget cycle for clinical studies be limited to three years. Successful achievement of well-defined and agreed-upon project goals would encourage further product development via submission of competitive proposals for continued research support. Imposing these time limits on funding cycles strengthens the product development process by necessitating scheduled gate reviews in which precise decisions are made to advance, halt, or extend same-stage investigations. Note that, in the review described in this report, one of the leading clinical studies requested funding for five years, and several of the ranked preclinical studies requested funding for three years. It is likely that offerors could subdivide their projects into aims having durations that fall within the expert panel's recommended funding cycles.

It was the opinion of the expert panel that, should the sponsor institute an annual grant competition for resuscitation fluid and adjunct therapy research, the sponsor could expect the quality of submissions to improve

over the coming years. Therefore, the expert panel suggested the sponsor consider funding three or four projects this coming year, expecting that some of these may prove to be ineffective or not relevant for military use and will be replaced by better projects in the next two or three years. The expert panel regarded funding one or more new grants each year as a means to advance resuscitation science by strengthening the review process and keeping investigators competitive and productive.

The sponsor should regularly evaluate funded research to assess the investigator's progress and to consider the value of funding further product development. Specific deliverables and demonstrations of an appropriate level of scientific and technological elements should be required periodically during the funding cycle, and a final demonstration of the deliverables should be required at the end of the program. This evaluation process should entail specific gate reviews at critical junctures and overall program reviews. Such reviews should differentiate between early *product* failures (*i.e.*, products that lack merit for the intended use) and *project* failures (*e.g.*, poor study management, inadequate enrollment, experimental design issues).

IV.1.2 Framing the categories of therapy

The expert panel regarded the development of blood volume expanders and/or compatible pharmacologic agents for hypotensive resuscitation as important categories of further research. In addition, the expert panel emphasized the importance of framing the military's product requirements so that future offerors might be able to more explicitly outline the military relevance of their products.

IV.1.2.1 Novel blood volume expanders, pharmacologic agents, and combination products

Investigators should be encouraged to develop novel fluids for blood volume expansion as a distinct category of therapy. While blood volume expanders are available for hypotensive resuscitation, the effectiveness of these conventional products may not be optimal. The expert panel regarded the creation of a more physiologic blood volume expander for use in hypotensive resuscitation as an important category of further research. Novel blood volume expanders that can partially or fully replace blood volume in combatants and can be titrated to a physiological endpoint are desirable. These blood volume expanders must have few, if any, contraindications for use and almost no limitations on dose so they could be used as needed for any wounded combatant.

In the current review, nine of the 22 ranked preclinical studies proposed the use of an augmented blood volume expander; three of these studies ranked in the top tier of preproposals. The expert panel suggested that the sponsor would benefit from receiving additional novel blood volume expanders in future preproposal submissions.

The expert panel advised the sponsor that wounded combatants with uncontrolled hemorrhage would likely need a pharmacologic agent in addition to the blood volume expander in order to improve survival rates. Potentially relevant novel pharmacological agents for administration by advanced first-responders include pharmacological agents that:

- Improve survival during the period of prolonged hypotensive resuscitation awaiting evacuation and during evacuation to surgical care, perhaps by reducing the volume of fluid required for blood volume replacement
- Limit organ system complications
- Improve long-term survival (survival during surgery and in the post-operative period)

The AFRRF Broad Agency Announcement (BAA) requested preproposals of resuscitation fluids and resuscitation fluid adjuncts, with the intention that these would be submitted as separate products. (See Appendix B.) However, several treatments proposed for review combined one or more pharmacologic/biological agents with a resuscitation fluid into a single product. This defined-combination formulation approach differs with the traditional approach of administering drugs with fluids or fluid vehicles in

a way that allows adjustments in the dosing rate tailored to individual patients. A defined-combination formulation of pharmacologic agent with fluid has more regulatory hurdles to overcome than separate pharmacologic agents and fluid components. The expert panel anticipated that combination products would need additional verification to assess whether the component pharmacologic agent was more effective in the proposed formulation than in other fluid vehicles.

From the perspective of a combat medic, a combination product would be more appealing than having to administer two or more separate products. However, the expert panel considered U.S. Food and Drug Administration (FDA) approval for such combination products difficult to achieve. Therefore, the expert panel believed that, in order to advance in development, a combination product would have to have compelling evidence of a unique advantage over that of the product's individual components.

The expert panel identified several target modalities of novel therapies as having the potential to improve survival from hemorrhagic shock on the battlefield (Table IV-1). For the purpose of this report, a cytoprotector was defined by the expert panel as a class of pharmacologic agents that might improve the resistance of cells to necrosis and apoptosis through a variety of mechanisms. A product having protective antioxidant properties and other cell-protective properties was classified as a cytoprotector rather than solely as an antioxidant. The expert panel regarded antibiotic therapy for resuscitation as less likely to affect patient outcomes than the categories listed in Table IV-1. Among the preproposals submitted, many that included anti-inflammatory agents were highly rated by the expert panel. One of the two leading clinical preproposals and eight studies in the top and middle tiers of preclinical preproposals included anti-inflammatory therapy.

Table IV-1 Example of treatment modalities for exsanguinating hemorrhage in combat. These have the potential to extend the period of survival during delays until surgical care, to decrease end organ complications, and to increase long-term survival.

Category of product
Anti-inflammatory
Antioxidant
Blood volume expander
Coagulation effector
Cytoprotector-nonspecific
Energy substrate
Hemoglobin-based oxygen carrier
Oxygen transport facilitator
Metabolic down-regulator

IV.1.2.2 Indications and product requirements for military relevance

Products used to treat wounded combatants with uncontrolled hemorrhage, whose systolic blood pressure is expected to average 50 to 60 mmHg for a two to four hour period during resuscitation, might differ from products used to treat cases in which hemorrhage is expected to be controlled and stopped within seconds of emergency care. The expert panel recommended that the sponsor identify, in detail, the indications the proposed product would treat with respect to the unique clinical conditions that occur in the combat situation. Defining the patient situation and/or the treatment target would facilitate focusing the proposed pharmacologic agents more explicitly on needed indications. The sponsor should precisely describe the condition of critical injury, uncontrolled hemorrhage, prolonged hypotension, and other details in the typical patient without being overly exclusive. Such characterization would limit the scope of treatment and refine the inclusion criteria to blood volume expanders and individual pharmacologic agents that could be administered in concert with

conventional hypotensive resuscitation before and/or after administration of resuscitation fluid, and contribute to the development of relevant experimental models.

To help offerors assess the potential military relevance of their proposed product, the initial AFRRF BAA listed some possible product requirements. (See Appendix B.) These were based on medical considerations and the logistical considerations of transport, storage, and utilization in combat field conditions. Products proposed in response to this request were to meet one or more of these requirements:

- Fluid-conservative treatment with hypotensive end-points
- Stable for prolonged periods at typical battlefield temperatures (less than or equal to 130°F, including less than 32°F)
- Provides supplemental oxygen-carrying capacity
- Mitigates or negates post-shock, post-resuscitation syndromes
- Compatible with blood products
- Easily and quickly administered by first-responder-medical personnel with limited training
- No mental or physical post-resuscitation impairment specific to the treatment

The expert panel recommended the sponsor re-visit this list of requirements for resuscitation fluids and adjunct therapies and specify both minimal product performance goals (*i.e.*, the military requirements) and optimal product performance goals. One such performance goal, not yet specified, is a weight and/or volume range per unit dose. Criteria for product stability and packaging are needed to evaluate military relevance. The product must withstand conditions of storage and transport without compromising its quality, purity, strength, or composition. The product must be in a form that can be easily and safely administered (*e.g.*, a single-use disposable that flows freely through an intravenous line.)

Specifying and prioritizing military requirements and optimal characteristics in the invitation letters for proposals and for future program announcements will help offerors assess the military relevance of their experimental products and tailor their products where possible. Having specific inclusion and exclusion criteria will also prevent the submission of proposals outside the scope of work.

IV.1.3 Framing the relevant experimental models

The expert panel expects that the traditional military product development pathway and FDA approval process will be followed in developing novel AFRRF therapies. A product's stage of development impacts the type of experiments undertaken and the review criteria imposed.

The intervention targets for AFRRF therapies should extend the interval of survival during prolonged evacuation, limit relative downstream morbidity as evidenced by the prevention or limitation of end organ damage, and decrease mortality. Experimental models should also test the efficacy and safety of AFRRF products for these same target outcomes.

IV.1.3.1 Recommendations for preclinical studies

The expert panel made several recommendations for preclinical studies that might indicate functionality of AFRRF products. It recommended the use of conscious animals to minimize artifacts resulting from anesthesia, which can obscure hemodynamic responses to treatment. Early preclinical models testing novel AFRRF products might include controlled and uncontrolled hemorrhage without anesthesia.

Compared to small animal studies, large animal models (*i.e.*, late-preclinical) are more likely to reflect functionality of the product in the combat environment. For AFRRF purposes, potentially relevant animal models for products in the late preclinical stage of product development might include:

- Two species of large animals
- Fluid-conservative treatment with hypotensive end-points
- Uncontrolled hemorrhage without anesthesia
- Uncontrolled hemorrhage and trauma (with anesthesia), to represent additional factors imposed by traumatic wounds
- Hypotensive resuscitation during prolonged periods, to represent the far-forward treatment interval in which the wounded combatant awaits evacuation to surgical care

Some animal models identified by the expert panel as less clinically relevant to hemorrhagic shock include:

- Isolated cell studies
- Models of vascular cross-clamping or other forms of mechanical flow interruption, because they fail to simulate the clinical situation
- Unrealistic reperfusion models, such as rapid re-infusion of the animal's own fresh whole blood
- End points that do not involve survival

Measures in preclinical animal models that are relevant to functionality in the combat environment include:

- Short-term survival (*e.g.*, 6 to 12 hours or longer) during conditions that simulate delayed evacuation to surgical care
- Prevention or limitation of end organ damage
- Long-term survival

Each candidate fluid has specific potential interactions that must be evaluated for potential additional harm to treated patients (*e.g.*, colloid solutions may induce or exacerbate blood coagulation abnormalities). Animal models useful to understanding factors related to concurrent care strategies include:

- Compatibility and effectiveness of the experimental treatment when used with a selection of other resuscitation fluids and/or drug products
- Possible variations of hypotensive resuscitative care

Although the expert panel discussed several aspects of preclinical studies that might improve their relevance for the military indication, there is no one animal model that is likely to predict or validate the use of a product in the military setting. Ultimately, the leading AFRRF candidates will need to be validated in human subjects for the indication of interest.

IV.1.3.2 Recommendations for human studies

The expert panel and LSRO agreed that while *in vitro* studies may aid in understanding the mechanism of action and animal studies may contribute interesting information to generate hypotheses, preclinical studies are an unreliable determinant of human health outcomes from new treatments.

The military indication for resuscitation fluid and adjunct therapies is a relatively unique situation. No parallel situation exists in the civilian population and data from civilian human clinical studies are not necessarily applicable to assess outcomes of resuscitation fluid treatment under combat conditions. Clinical studies conducted outside the military theatre of operations are not likely to represent the limited training and experience of advanced first-responders on the battlefield or the prolonged periods of hypotensive resuscitation of the wounded combatant awaiting evacuation to surgical care. As a result, short of doing studies in combat, it would be difficult to prove the efficacy of a novel AFRRF product expressly for combat indications.

As discussed in Chapter I, warfare is rapidly changing. No one civilian study will represent the varied situations and experiences of wounded combatants. Depending on the area of the combat and the type of combat, hemorrhage might result from blast wounds from bombs, burn injuries, high- or low-velocity gunshot

wounds, crush injuries from vehicles, and knife wounds from hand-to-hand combat. Hemorrhage from extremity wounds results in nearly one-tenth of all combat deaths, but improved treatments addressing these types of injuries may reduce fatalities (Champion *et al.*, 2003).

When deciding upon a surrogate model to reflect far-forward military situations, the expert panel considered the types of traumatic injuries occurring in the United States as well as the frequency of those injuries where medical research is conducted. For these reasons, the expert panel regarded the best overall surrogate model in the U.S. civilian sector for treatment of combat inflicted hemorrhage to be the use of AFRRF products by civilian first-responders (*e.g.*, emergency medical technicians) to treat extensive blunt trauma, such as extremity injuries resulting from motor vehicle accidents. Because of a lower rate of incidence, the expert panel regarded use of AFRRF products by emergency medical technicians to treat high-velocity penetrating trauma (*i.e.*, assault-weapon wounds) as the second-best overall surrogate model for treatment of combat inflicted hemorrhage in the civilian sector. The expert panel viewed low-velocity gunshot wounds from handguns and stab wounds as less clinically relevant.

The expert panel regarded long-term survival to 28 days and to 60 days to be meaningful and unambiguous endpoints for evaluation of treatment of hemorrhagic shock. The expert panel also suggested that improved short-term survival of the wounded combatant awaiting evacuation to surgical care is a worthy goal of AFRRF and adjunct therapies. Clinical AFRRF studies should also measure coagulation profile, neurological status, and end organ failure. The coagulation system is prone to dilution and other effects from resuscitation. Neurological measures are important to determine severity of shock and/or identify concurrent neurotrauma. A successful treatment would achieve and maintain optimal organ function.

The expert panel surmised that several obstacles, as discussed in the Introduction to this report, might deter the development of resuscitation fluid products for use by military personnel under combat conditions. The expert panel underscored two challenges in particular. First, products that afford the best utilization by the military might not be available for use. For example, resuscitation fluid products and adjunct therapies delivered intravenously may be more commercially viable than those administered via intranasal or intraosseous routes. Yet, the latter have potential for military application. Second, the military may have difficulty obtaining data needed for FDA approval of a product for resuscitation therapy. While supportive clinical data under conditions of prolonged evacuation might be obtained by conducting studies with populations in other countries that face warfare and/or other situations of mass casualties, obtaining such data is highly improbable and, even if available, is unlikely to earn FDA approval for a military indication. Although the expert panel acknowledged the difficulty of evaluating the scientific validity of various treatment options in the face of not being able to carry out the critical experiments under realistic conditions, it nonetheless encouraged the military to conduct Phase II and Phase III trials of resuscitation products under combat conditions with informed consent of those who are deployed to combat.

IV.1.4 Further research to advance resuscitation science and improve survival from combat injuries

Fundamental questions must be answered in order for substantial advances to be made in resuscitation science. The value of a novel therapy that is demonstrated to improve survival under controlled circumstances is limited in real-life application unless medical care concurrent with its administration is appropriate and adequate.

IV.1.4.1 Framing basic questions

Given the limited resources available to the combat medic in battlefield circumstances, it is critical to define how a medic would decide to administer a product and how to monitor the sufficiency of resuscitative care. Modest amounts of resuscitation solutions will be administered on the battlefield to restore some level of perfusion short of complete restoration of blood pressure. The optimal blood pressure to achieve during

resuscitation of the wounded combatant has yet to be ascertained. Therefore, the optimal amount of a blood volume expander that should be administered by the advanced-first responder has yet to be validated.

Determining answers to these and other fundamental questions would advance our understanding of the conditions and factors that would increase survival rates of wounded combatants treated with hypotensive resuscitation fluids in combat situations. The expert panel proposed that the sponsor organize a two- or three-day theories meeting of experts to identify improvements in methodologies critical to resuscitation science investigations. This gathering of experts should address the following questions:

- Possible variations of hypotensive resuscitative care
- What is adequate and optimal blood volume expansion?
- What are the appropriate endpoint(s) for measures of blood volume expansion?
- What is the best noninvasive measure of tissue perfusion and oxygenation?
- What is adequate and optimal tissue oxygenation?
- What are the appropriate endpoint(s) for measures of tissue oxygenation?
- What secondary endpoints are predictive of efficacy and survival?
- Can current practices to discern the need for resuscitation fluid and adjunct therapies be further improved to achieve optimal tissue perfusion?

IV.1.4.2 Framing the environment for resuscitative care

LSRO was not charged with assessing the current capability of advanced first-responders to deliver AFRRF treatment on the battlefield. Therefore, the expert panel did not investigate the readiness of the military to introduce a novel AFRRF product nor evaluate the broader spectrum of combat casualty care. Nevertheless, the expert panel recognized the complex military environment in which AFRRF therapies are used and that the effectiveness of AFRRF therapies can be impacted by several confounding factors such as the warfare environment and point-of-care issues (See Introduction, section I.3). Even if new resuscitation fluids and adjunct therapies are developed with the capacity to improve survival and decrease morbidity, they must be used in an environment that also improves the process of combat casualty care.

As discussed in the Introduction (section I.3.3.1), combat medics are not trained to the level of a civilian emergency medical technician, except for medics in the Special Forces, and combat lifesavers typically receive three days of first-aid instruction (Cloonan, 2003). Greater training of advanced first-responders in point-of-care issues will support optimal outcomes in patients at risk for hemorrhagic shock. Such point-of-care issues might include additional training in collecting and monitoring simple measures, assessing and triaging patients, and obtaining intravenous access. As recently suggested by Parsons (2005), further training and equipment to clear airways and intubate the patient might also be vital for improved survival. Additional improvements in survival might also be achieved by technological innovations in devices, such as those designed to assist the first-responder in gaining better intravenous access.

IV.2 RECOMMENDED PROCESSES AND FORMS FOR PROPOSALS

LSRO and the expert panel specified recommendations for instructions and forms that the sponsor might use for future preproposals and proposals. Such recommendations are intended to assist the sponsor in obtaining information and data useful for scientific peer-review, evaluation of military relevance, and assessment of product commercial viability.

IV.2.1 Recommendations for future preproposals

At present, the USAMRMC website (2005) accepts continuous online submission of preproposals at: <http://www.usamraa.army.mil/pages/tatrc/02baapre.cfm>.

Similarly, preproposals are accepted in response to special announcements, such as the AFRRF announcement for the review outlined in this report. These preproposals, however, are subject to deadlines and other requirements indicated in those special announcements.

The USAMRMC BAA Preproposal Form for online submission and similar instructions for preproposals, located in Appendix-2 of the USAMRMC instruction packet, accommodate a wide range of submission topics (U.S. Army Medical Research & Materiel Command, 2005). Currently, offerors are instructed to provide contact information and brief summaries for each section of the preproposal using a defined space that accommodates a maximum of 4000 text characters (approximately one page) for each of these preproposal sections:

- Problem to be studied
- Significance and/or uniqueness of the proposed effort
- The potential military relevance
- Duration of project to be studied and estimated cost of project
- Participating personnel, their title, role, and percentage of effort
- Major capital equipment/subcontracts exceeding \$10,000 (optional)
- Brief description of animal and/or human use
- Conclusions
- Brief curriculum *vitae* of key personnel
- List of relevant publications

In lieu of a general preproposal format, the AFRRF BAA for the review outlined in this report required responses be limited to a total of five pages and contain the following information and data to the extent that they were available:

- Description of the candidate technology/product and whether the product is approved for other uses
- Summary of supporting *in vitro*, preclinical, and clinical data that validate the benefits/utility of the proposed product
- Description of the mode of action
- Inclusion of any safety evaluations that had been conducted and additional studies underway or planned for the near-future
- Discussion of schedule considerations for how soon the product would be ready for human clinical trials and whether Phase III funding is available

For future AFRRF preproposals, additional instructions concerning product specifications for military relevance and for presentation of scientific materials are needed to ensure that offerors prepare AFRRF preproposals that are useful. The expert panel advised the sponsor to continue using forms to guide the content areas and define the space limits of preproposal submissions. The expert panel also recommended that AFRRF preproposal instructions and forms be similar to full AFRRF proposals with respect to content areas, except that more stringent page limits should be imposed for preproposals (Table IV-2). LSRO and the expert panel recommended that the preproposal be made shorter than the proposal by limiting the description of the proposed product/agent to one page, limiting the research plan to four pages, and limiting biographical sketches to two pages for each individual. LSRO and the expert panel further recommended that AFRRF instructions and forms for future preproposals and proposals contain the major sections in the order listed in Table IV-2.

IV.2.2 Specified format and content areas

The expert panel made recommendations for a template with specific blanks for every offeror to complete that can help obtain minimal but consistent and required data in all proposals submitted. Standardized formats for the proposal packet increase the efficiency of the scientific review process. Reviewers become familiar with the organization of information so that required information can be readily located and missing information can be

identified. Moreover, the offeror is less likely to omit necessary information if it is requested on the proposal form with an accompanying space reserved for it.

The existing USAMRMC BAA general requirements for proposals share many similarities with the requirements of Public Health Service Grant form 398 (PHS 398) used by NIH (U.S. Army Medical Research & Materiel Command, 2005; U.S. Department of Health and Human Services, 2004).

Drawing on the experience reviewing the AFRRF preproposals and earlier experiences with the NIH review process, the members of the expert panel tailored a specific proposal packet for the USAMRMC AFRRF awards program. These forms include the existing USAMRMC general forms for proposal submissions along with modifications and supplements that are meant to comply with USAMRMC submission requirements (U.S. Army Medical Research & Materiel Command, 2005). Appendix F describes the suggested AFRRF proposal instructions in detail. This Appendix also includes copies of eleven formatted sections (Forms A-K) that the sponsor might provide to offerors to prepare their AFRRF proposals. (Note that the copies of forms in this report were modified in size and margins to fit the LSRO report formatting requirements and are not approved for actual submission purposes. Forms in Microsoft® Word format will be provided to the sponsor as a supplement to this report.)

To ensure that the suggested AFRRF proposal instructions and forms are consistent with military regulations and procedures, USAMRMC and the U.S. Army Medical Research Acquisition Activity (USAMRAA) may need to further modify them prior to their distribution to offerors. Most components of the recommended proposal are generic and can be easily modified to accommodate additional areas of research and future changes in the research focus of CCCRP.

Table IV-2 Forms, recommended page limitations, and related specifications.

<u>Section</u>	<u>Form</u>	<u>Page Limit, Proposal (Preproposal)</u>	<u>Related Specifications</u>
Proposal Cover Page	A	1	Do not exceed 120 characters in the title of research project, including the spaces between words and punctuation
Abstract, Performance Sites, Key Personnel, Other Significant Contributors	B	None	<u>Abstract must not exceed space provided on Form B</u>
Table of Contents	C	None	
Statement of Work	D	1	
Product/Agent	E	2 (1)	
Military Relevance of Product/Agent	F	1	
Research Plan	G	Total = 8 (4) 2 (1) 2 (1) 4 (2)	Page limits are for all text, figures, charts, tables, and diagrams included in the Research Plan.
Specific Aims, Background, and Significance sub-section limit:			
Preliminary Data sub-section limit:			
Research Design and Methods sub-section limit:			
Research Bibliography	None	None	<u>Each continuation page must bear the heading: Research Bibliography</u>
Acronym, Symbol Definition	None	None	
Detailed Cost Estimate for Initial 12 Month Budget Period	H	None	
Summary Budget for Entire Proposed Period of Support	I	None	
Budgets Pertaining to Consortium/Subawards	H/I	None	
Biographical Sketches of Key Personnel and Other Significant Contributors	J	3 (2) per individual	
Existing/Pending Support and Past Related Efforts	None	None	

(continued next page)

Table IV-2 (continued)

<u>Section</u>	<u>Form</u>	<u>Page Limit, Proposal (Preproposal)</u>	<u>Related Specifications</u>
Consortium/Contractual Arrangements for Proposed Research	None	None	
Letters Confirming Collaboration	None	None	<u>(Full proposals only)</u>
Available Facilities and Major Equipment	K	None	
Institution Safety Program Plan	Available	None	<u>(Full proposals only)</u> See Appendix 11 of the USAMRMC general proposal instructions and forms.*
Certificate of Environmental Compliance	Available	None	<u>(Full proposals only)</u> Submit one certificate for each site conducting research under the proposal, including subcontractors. See Appendix 8 of USAMRMC general proposal instructions and forms.*
Human Use Required Information and Approval	Available	None	<u>(Full proposals only)</u> See Appendix 9 of the USAMRMC general proposal instructions and forms. Must be submitted within 60 days of award if proposal is approved for funding.*
Animal Use Required Information and Approval	Available	None	<u>(Full proposals only)</u> See Appendix 10 of the USAMRMC general proposal instructions and forms. Must be submitted within 60 days of award if proposal is approved for funding.*
Appendix	None	None	<u>(Full proposals only)</u> Appendix material might not be reviewed. Hence, do not include in the Appendix experimental data or other information critical to the review. <u>Do not use the Appendix to circumvent the page requirements of the body of the proposal.</u> Indicate conclusion of Appendix material with a line stating "END OF APPENDIX MATERIAL"

*http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm (U.S. Army Medical Research & Materiel Command, 2005)

In making their recommendations, LSRO and the AFRRF expert panel considered possible options that the sponsor might use for distributing proposal instructions and forms and for the collection and processing of the completed proposals. All features of the recommended AFRRF proposal are amenable to paperless transactions such as submission of compact disk (CD) files by mail or submission of the proposal through a USAMRAA Uniform Resource Locator (URL). Once instructions and forms are approved by the sponsor for official use, they could be posted on-line as both Microsoft® Word files and as portable document format (PDF) files for downloading by individual offerors.

IV.2.2.1 Recommendations and the current USAMRMC format

The expert panel advised that AFRRF preproposals and proposals have specific requirements in addition to the general USAMRMC submission requirements.

The current USAMRMC instructions for completion of preproposals and proposals indicate that awards are typically for a three year period and in no case can exceed five years. As discussed in section IV.1.1.3, the expert panel encouraged the sponsor to fund specific proposals for limited cycles and to subject previously funded offerors to a competitive application process for new proposals. The expert panel recommended that budget periods for AFRRF preclinical studies be limited to two years and clinical studies be limited to three years. Additional support can then be sought to build upon successful achievement of study goals.

The expert panel thought it helpful to identify the proposed type of study on the research proposal cover page (*i.e.*, clinical or preclinical). The expert panel prefers that USAMRMC adopt the PHS 398 format of listing sites of research, key personnel, and other significant contributors immediately after the abstract so that this information is available to reviewers in a prominent location.

Neither NIH nor USAMRMC require that offerors submit information on the experimental product/agent in as much detail as the expert panel determined was meaningful for reviewing AFRRF preproposals and proposals. To address this information gap, the expert panel outlined specific product information that should be submitted and created a form that the sponsor may wish to include in its proposal packet. (See section IV.2.2.2.) For AFRRF submissions, the offeror must compare their product/agent with the sponsor's stated military requirements for combat use. Furthermore, the offeror should indicate how the product is expected to substantially improve survival from exsanguinating hemorrhage. (See section IV.2.2.3.)

The USAMRMC currently limits the body of the proposal (*i.e.*, Research Plan) to 20 pages. The expert panel recommended more stringent page limits. As indicated in Table IV-2, the recommended limits on the Research Plan are eight pages for proposals and four pages for preproposals. A form was designed for the Research Plan that defines the major sections required for inclusion and specifies the page limits for each section. (See Appendix F.) In the Research Plan, the offeror discusses specific aims and hypotheses to be tested, background and significance, preliminary data, research design and methods (*i.e.*, the type and number of subjects, the measurements and endpoints, and how the data will be collected), and indicates statistical protocols and analysis. The preliminary data should demonstrate that the product can be administered under the circumstances proposed. The offeror is instructed to explain how the proposed experimental model is relevant for supporting clinical use of the product under combat conditions. Furthermore, the expert panel suggested that a timetable for completion of the proposed project within the funding period be provided by the offeror.

IV.2.2.2 Identification and characterization of the product/agent

The expert panel determined that many of the AFRRF preproposals received did not adequately characterize the experimental product/agent. The expert panel created a form that specifies exactly what product information should be included in the preproposal/proposal and advises that this information be placed after the Statement of Work and ahead of the Military Relevance sections in the preproposal/proposal (See Figure IV.1.). The expert

panel suggested that future reviewers would benefit from being able to identify and understand the product/agent proposed for investigation prior to reading and evaluating the Research Plan.

Principal Investigator/Program Director (Last, First, Middle):

Product/Agent	
Do not exceed a total of 2 pages for Form E including the continuation page if needed for full proposals or 1 page for preproposals. The citations for publications referred to on Form E should be listed in the Research Bibliography.	
PRODUCT IDENTITY (and formulation):	
PRODUCT CHARACTERIZATION Physiochemical properties (e.g., potency, long-term stability, temperature for storage/transport, solubility, stability after reconstitution): Pharmacokinetics (bioavailability/absorption, distribution, half-life, metabolism, clearance/excretion):	
ADMINISTRATION (route, preparation, volume per unit dose):	
SAFETY DATA (brief overview):	
PHARMACODYNAMICS AND MECHANISM OF ACTION (for treatment of exsanguinating hemorrhage, e.g., volume expander):	
PROVIDE A TIMELINE OF PRODUCT DEVELOPMENT (from current stage to first/next clinical phase): Is product/agent currently in U.S. market? No <input type="checkbox"/> Yes <input type="checkbox"/> If yes, by what route of administration and for what indication(s)? If no, does product/agent have investigational new drug (IND) status for any indication?	
PRODUCT MANUFACTURER: Letter of support from corporate partner included in this proposal: No <input type="checkbox"/> Yes <input type="checkbox"/> Estimated cost range per dose:	
INTELLECTUAL PROPERTY PROTECTION RIGHTS/CONTRACTS (e.g., patents):	
OUTLINE PROCESS FOR COMMERCIAL DEVELOPMENT: Is the product/agent sufficiently attractive to industry that it will be commercially viable outside the military environment? What is the plan for taking the product/agent to market?	

AFRRF (Rev. 2005)

Page

Form E

Figure IV.1 Product/agent form. See Appendix F for related instructions and proposal forms. Note that the copies of forms in this report were modified in size and margins to fit the LSRO report formatting requirements and are not valid for actual submission purposes.

The following information should be included in the product/agent section of future preproposals/proposals and would be limited to two pages for proposals and one page for preproposals:

- Identity and formulation
- Characterization
- Route of administration
- Safety data
- Pharmacodynamics
- Timeline of product development to obtain regulatory approval
- Manufacturer
- Intellectual property information
- Commercial development plan

In the product characterization section, the offeror would describe the physiochemical properties of the product and address such characteristics as potency, solubility, and stability. These characteristics are particularly useful for assessing the product's military relevance. (See section IV.2.2.3.) Likewise, the pharmacokinetics of the product/agent would be described, specifically the agent's bioavailability, distribution, half-life, metabolism, and excretion.

Product administration must also be addressed, such as requirements for preparation, route of administration, and volume per unit dose. A brief summary of the safety data should also be included. Of particular interest is whether there is a biohazard from expired, crushed/damaged, leftover product. The offeror should mention if the product requires special storage, transport, or use conditions.

Of particular interest to future reviewers would be an explanation of the known or hypothesized pharmacodynamic mechanism of action for the treatment of exsanguinating hemorrhage. Of interest to the sponsor would be an outline of product development to obtain FDA approval from current product development stage to the next logical clinical phase (*e.g.*, first human clinical trial). This timeline of product development is distinct from the tentative timetable for the proposed project in the Research Plan. The offeror should succinctly state how the proposed project will further the product/agent's development.

Finally, the offeror should indicate whether the product manufacturer is providing a letter of support (full proposals only) for the proposed project and specify relevant contractual issues of the focal products/agents, such as patents. This information is vital to determine whether the offeror has industry partners and expertise to develop the product commercially if the product performs as hypothesized. The expert panel decided that it would be instructive for the offeror, future reviewers, and the sponsor if the offeror would outline the process for commercial development of the product/agent. One expert panel member or an individual identified by the sponsor might be designated to provide a commercial assessment for all proposed projects.

IV.2.2.3 Military relevance of product/agent

A one-page section of the preproposal/proposal should discuss the military relevance of the product/agent using information supplied in the previous section. Here the offeror should assess the strengths and limitations of use of this product/agent compared to military product requirements or performance goals specified in the BAA or Request-for-Information to which the offeror is responding. For example, the offeror should consider shelf-life/stability under extreme environmental conditions, the effect of the product's weight and volume per unit dose on the soldier who transports it, and the safety and ease of use by first-responders on the battlefield.

The offerors should state whether this product will increase the probability of survival from exsanguinating hemorrhage on the battlefield and/or decrease later medical complications. They should also discuss how patients will be selected for product administration.

IV.2.2.4 Protection of human subjects

The peer review process should include careful consideration of the protection of human subjects from the risks of research. For studies that plan to enroll subjects without individual informed consent (*i.e.*, enrollment during the pre-hospital phase of emergency care) the review should include assessment of potential obstacles that might impede the experimental treatment from realistically securing “community consent” (*i.e.*, approval by representatives of the community charged with evaluating product safety data). Moreover, the review of proposed clinical trials should include consideration of the proposed Data and Safety Monitoring Plan for providing oversight and monitoring of the safety of participants and the validity and integrity of the data.

USAMRMC does not require Institutional Review Board approval and certification of proposed research prior to review of proposals. However, Appendix 9 of the USAMRMC proposal instructions contains information pertinent to the required review and approval process for research involving human subjects and “anatomical substances.” Required materials must be submitted within 60 days of an award if the proposal is approved for funding (U.S. Army Medical Research & Materiel Command, 2005).

IV.2.2.5 Justification of the proposed animal model

Similar to requirements for completing PHS 398 (2004), LSRO and the expert panel recommended that offerors planning to use vertebrate animals should provide the following information in their research plan:

- Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work
- Justify the use of animals, the choice of species, and the numbers to be used

In addition, the offerors should:

- Discuss how the proposed animal model is relevant to the military clinical condition (*e.g.*, hemorrhagic shock)
- Measure survival as an endpoint

USAMRMC does not require Institutional Animal Use and Care Committee approval and certification of the proposed research prior to review of proposals. Appendix 10 of the USAMRMC proposal instructions contain explicit information pertinent to the required review and approval process for research involving vertebrate animals (U.S. Army Medical Research & Materiel Command, 2005). Required materials must be submitted within 60 days of an award if the proposal is approved for funding.

IV.2.2.6 Additional format considerations

The sponsor should consider accepting 11 point font size in addition to the 12 point size now required by USAMRMC for proposal submission, similar to the font requirements for PHS 398 (U.S. Department of Health and Human Services, 2004). PHS 398 also only accepts the Arial, Helvetica, Palatino Linotype, and Georgia fonts whereas USAMRMC does not currently specify a requirement for font type. The sponsor might consider instructing offerors to select one of those fonts as well.

To facilitate identification of the individual pages in the proposal packet, a running header of the principal investigator’s or program director’s name is suggested for each page of the proposal. Finally, the AFRRF proposal is formatted in the style of PHS 398 in that all important components are included as pages in the body of the proposal, in contrast to the current USAMRMC format of organizing some key materials, such as biographical sketches and descriptions of equipment and facilities, as addenda.

IV.2.3 Public announcements and other communications

The successful development of an AFRRF product will be enhanced by announcement and proposal processes that adequately attract and inform potential offerors, and accommodate an efficient and timely distribution of proposal instructions and collection of completed proposals.

IV.2.3.1 Guidance for future Broad Agency Announcements

The expert panel recommended the sponsor use a standing committee or peer-review panel for guidance on the contents of BAAs and other requests for submission of future AFRRF preproposals. A standing committee would ensure that offerors receive sufficient information about the content upon which their proposals will be evaluated; this increases the likelihood that proposals will contain the necessary information required for review decisions. Future expert panels might also specify additional formatting instructions to increase the efficiency of their review processes.

IV.2.3.2 Website for AFRRF research

CCCRP should consider developing a website to provide information to those interested in applying for AFRRF awards. Such information might include a list of product/agent categories of past submissions and examples of methods that have been used for peer-review of proposed research. Information about other projects that have been funded under the AFRRF award program could also be provided.

The proposal abstract serves as a succinct description of the proposed work when separated from the proposal. Thus, USAMRMC should mount the abstracts of funded projects on its website to promote the AFRRF research program, and to serve as examples for future offerors.

Links should be set-up on the website to enable the download of proposal instructions, forms and other information as well as establishing links to future funding opportunities offered by the ONR (http://www.onr.navy.mil/sci_tech/personnel/prop_submission.asp).

At present, proposals to USAMRMC can be submitted by courier, mail or hand-delivery as electronic documents on CD and digital versatile disc (DVD). The USAMRMC website does not currently accommodate electronic submission of full proposals. However, some USAMRMC award programs do accept electronic submission of proposals in the form of PDF files through the Office of the Congressionally Directed Medical Research Programs eReceipt system. An AFRRF website could be designed to accept submission of research proposals via the USAMRMC system, thus streamlining and simplifying the proposal submission process, without losing the opportunity to tailor the information obtained for specific awards.

IV.2.3.3 Database of interested parties

The expert panel encourages the sponsor to utilize and expand the database of interested parties begun by LSRO to build a network of investigators, experts, and other individuals involved with resuscitation fluid science. Such a network is a resource that the sponsor can mine for speakers to share ideas at meetings, experts to serve on review panels, investigators to furnish competitive proposals, and instructors to educate the sponsor in new technologies.

IV.2.3.4 Point-of-contact experts and other communications

Offerors who submitted preproposals in response to the AFRRF BAA described in this report indicated to LSRO that six to eight weeks between the receipt of an invitation for proposal submission and the deadline for submission would be adequate. They also indicated that it would be helpful if the sponsor were to have several

knowledgeable point-of-contact individuals to answer questions. The sponsor might consider retaining one administrative individual to handle general administrative questions as well as one clinical, one preclinical, and one military content expert.

IV.3 RECOMMENDATIONS FOR FUTURE PEER REVIEW

IV.3.1 Expert panel

The expert panel recommended that a multidisciplinary panel of experts conduct future reviews. Future peer-reviewers should minimize potential conflict-of-interest by excusing themselves from participation in the review and ranking of AFRRF preproposals/proposals from (a) their institution, (b) by researchers they have collaborated with during the past three years, and (c) by individuals with whom they have/had a mentor relationship.

IV.3.2 Preparation for review

The expert panel recommended that future peer-reviewers conduct the initial review of preproposals/proposals that fall within their area of expertise and research interests. Future peer-reviewers should sort preproposals/proposals into preclinical or clinical categories for review purposes.

IV.3.3 Review criteria for preproposals and proposals

The expert panel recommended that future peer-reviewers use its initial review form (Figure III.3) and scoring methods for military relevance and scientific merit (section III.3.2) as resources to formulate review methods for future reviews.

Depending on the number of preproposals or proposals under consideration, future peer-reviewers may need to utilize lead reviewers to distribute the work load and prioritize the applications. Lead reviewer scoring, after discussion with the expert panel, can be used to eliminate from further review those preproposals/proposals determined to lack sufficient military relevance and/or scientific merit.

The expert panel recommended that those preproposals/proposals determined by lead reviewers to have sufficient military relevance and scientific merit be further scored by the full expert panel and then ranked by the panel's scores. (See section III.3.2.)

The expert panel suggested that the sponsor forward a copy of the individual preproposal critique to the respective offeror to assist the offeror in their preparation of full proposals or re-submission of preproposals.

IV.3.4 Leading candidates

In general, the expert panel gave investigators the benefit of the doubt when information was missing from the preproposal. The expert panel expected that some studies whose preproposals were scored highly might fall in ranking when the full proposals are reviewed. Other highly ranked studies might not be selected by the sponsor for funding for other reasons, such as cost or projected time delays before the study can begin. Therefore, LSRO and the expert panel encouraged the sponsor to request more proposals than the sponsor intends to fund.

At a minimum, the sponsor should consider requesting proposals for the two leading clinical candidates and for the 14 preclinical preproposals that scored in the top and middle tiers of total score. The expert panel estimated that a review and ranking of these 16 proposals could be completed by a peer-review panel in a one-day meeting if the sponsor followed its recommendations for the format and content of proposals. (See section IV.2.)

IV.4 SUMMARY

IV.4.1 Recommendations for the framework for reviewing proposals

The expert panel and LSRO recommended that the sponsor:

- Extend the funding commitment to the AFRRF program beyond 2011 for the development of an improved AFRRF product
- Rely on a multidisciplinary standing committee of experts to provide guidance for future BAAs and for the evaluation of future preproposals. Additional review panels or *ad hoc* reviewers may be needed for review of proposals
- Limit budget periods for specific AFRRF project proposals to a maximum of two years for preclinical studies and to three years for clinical studies with the potential for additional funding if the project is on track and successful
- Distinguish between two product categories for investigation, encouraging investigation of novel fluids for blood volume expansion as well as emphasizing the need for novel pharmacologic agents that can be used with or without various resuscitation fluids
- Define the specific indication for the proposed product by listing clinical conditions of the targeted patient population
- Define minimal and optimal product performance goals (*i.e.*, requirements) and prioritize the product performance goals
- Request proposals for the two leading clinical candidates and for the 14 preclinical preproposals that scored in the top and middle tiers in the current review
- Consider developing a website to provide information to those interested in applying for AFRRF awards
- Organize a meeting of experts to identify improvements in methodologies critical to resuscitation science investigations
- Study the adequacy of first-responder medical training

The expert panel recommends that future peer-reviewers:

- Minimize potential conflict-of-interest by excusing themselves from participation in the review and ranking of AFRRF preproposals/proposals from their institution, by researchers they have collaborated with during the past three years, and by researchers with whom they have/had a mentor relationship
- Sort preproposals/proposals into clinical or preclinical categories for review purposes
- Conduct the initial review of preproposals/proposals that fall within their area of expertise and research interests
- Use the initial review form and scoring methods developed by the AFRRF expert panel as resources to formulate methods pertinent to the review at hand
- Rank preproposals/proposals by individual scores rather than by direct comparisons among submissions

IV.4.2 Recommendations for future proposal processes and forms

The expert panel and LSRO recommended that the sponsor:

- Format a standardized packet for use by those submitting future AFRRF preproposals and proposals
- Require that future preproposals and proposals contain sections for product identification and characterization and a discussion of the military relevance of the product
- Impose stringent page limits for preproposals and proposals
- Share with offerors the guidelines for how preproposals and proposals will be reviewed and, after the review, forward to offerors a copy of the study critique prepared by the expert panel

- Have several knowledgeable point-of-contact individuals to answer questions about the proposal process

IV.4.3 Recommendations for experimental models and clinical studies

The expert panel and LSRO recommended that future offerors, peer-reviewers, and the sponsor consider that:

- Preclinical AFRRF studies should include non-anesthetized models to study hemorrhage alone and an anesthetized model to study uncontrolled hemorrhage plus trauma
- Preclinical AFRRF studies should measure short-term survival during conditions that simulate delayed evacuation to surgical care, and should measure end organ damage and long-term survival
- The best surrogate model for treatment of combat inflicted hemorrhage is the use of AFRRF products by civilian emergency medical technicians to treat extensive blunt trauma
- Clinical AFRRF studies should measure coagulation profile, neurological status, end organ failure, and survival to 28 days and to 60 days
- Leading candidates should be validated under battlefield conditions

V. CONCLUSIONS

V.1 SUMMARY OF KEY FINDINGS

V.2 SUMMARY OF PRINCIPAL RECOMMENDATIONS

V. CONCLUSIONS

The expert panel reviewed 59 advanced first-responder resuscitation fluid (AFRRF) preproposals and attempted to balance the weight given to military relevance and scientific merit. The degree to which the preproposal met the military's intended purpose of reducing mortality in extended evacuation situations and increasing long-term survival was considered as a component of military relevance. The expert panel identified several leading candidates of sufficient merit for further review of a detailed full proposal.

The expert panel also made suggestions to develop a framework for a research program to further evaluate and prioritize current and future AFRRF technologies, and to improve the quality of future proposals for the likelihood that such studies will advance development of AFRRF products for military use.

V.1 SUMMARY OF KEY FINDINGS

Numerous products are under development having the potential for use in civilian resuscitative care and several of these may meet the extraordinary demands required of products under combat conditions to treat exsanguinating hemorrhage. The Life Sciences Research Office, Inc. (LSRO) identified 48 unique experimental products among the 59 preproposals under consideration, which included coagulation effectors, strategies targeting cardiovascular responses and/or enhancing oxygen delivery, cytoprotectors supporting cell structure and metabolism, strategies that are purported to minimize inflammation and/or favorably modulate immune response, and products for blood volume expansion and other purposes.

The expert panel identified two qualifying candidates from among the ten clinical AFRRF preproposals submitted. Leading preclinical preproposals were also identified: a group of five top-tier preclinical preproposals and a second group of nine that scored the next best in ranking from among 49 preclinical AFRRF preproposals submitted. The preclinical candidate with the best total score also ranked best in both military relevance and scientific merit. The five top preclinical preproposals had better scores for military relevance and scientific merit than the two clinical preproposals.

Several preproposals of anti-inflammatory treatments rated highly. Specifically, one of the two clinical proposals and seven of the top ten preclinical proposals included anti-inflammatory therapies.

Of particular concern to the expert panel was the number of submissions of combination products, which may have been the result of the wording of the AFRRF Broad Agency Announcement. Products that combined one or more pharmacologic agents with a blood volume expander in a defined formulation, for example, contrast with the traditional approach of administering drugs and fluids in a way that allows for adjustments in the dosing rate of each, tailored to individual patients. Moreover, such defined-formulation combination products have greater regulatory hurdles to overcome than do the separate components. The expert panel anticipated that such combination products would need verification to assess that the pharmacologic components were more efficacious in the defined formulation than when used in other fluid vehicles.

The two top preclinical candidates were estimated to be within four years of human clinical trials at best and the remaining three candidates in the top tier were estimated to be five or more years from human clinical trials. One product, an augmented blood volume expander, is at best two years from clinical trials; its total score ranked 6th place for preclinical preproposals.

Assuming the products perform as hypothesized, the non-military market potentials for the top three preclinical products were rated highly. The remaining two preclinical candidates in the top tier were assessed as having moderate commercial appeal. For the two clinical candidates, one is already approved by the U.S. Food and Drug Administration (FDA) for use in surgery and the other agent, should it prove to be an effective therapy, was estimated to be moderately viable in the commercial market.

AFRRF products that have military relevance or that can be modified to be militarily relevant, yet whose corresponding preproposals were evaluated as currently insufficient represent a pool of potential products for future development if new preproposals for these products offer sufficient scientific merit.

LSRO prepared critiques of each of the 59 preproposals for the sponsor using the brief summaries by the two lead reviewers supplemented with comments of the expert panel. The critiques reflect some, but not all, of the preproposal strengths and weaknesses as discussed by the expert panel.

V.2 SUMMARY OF PRINCIPAL RECOMMENDATIONS

A summary of the principal recommendations of LSRO and the expert panel is presented in Table V.1 along with the rationales for the recommendations.

One important contribution of the AFRRF expert panel was the creation of a standardized format for including detailed information on the proposed experimental product, which will assist reviewers in assessing military relevance. (See Figure IV.1.) Of particular interest to future reviewers is the instruction to the offeror (applicant) to characterize the product/agent's stability, to explain the known or hypothesized pharmacodynamic mechanism of action for the treatment of exsanguinating hemorrhage, to include a projected outline for product development to obtain FDA approval, and to summarize the anticipated process for commercial development of the product/agent. Also, on an additional proposed form, the offeror must compare their product/agent with the sponsor's stated military requirements for combat use. Furthermore, the offeror should indicate how the product is expected to substantially improve survival from exsanguinating hemorrhage. (See section IV.2.2.3.)

To expedite the submission of full proposals, LSRO and the expert panel prepared AFRRF proposal instructions and forms that were designed to comply with current U.S. Army Medical Research and Materiel Command (USAMRMC) requirements. (See Appendix F.) Additional formatting suggestions the sponsor should consider are to liberalize font size to 11 point and specify font types for the offeror. To facilitate identification of the individual pages in the proposal packet, a running header of the principal investigator's or program director's name is suggested for each page of the proposal. Finally, it is recommended that the AFRRF proposal is formatted in the style of Public Health Service Grant form 398 (PHS 398) in that all important components of the packet are included as pages in the body of the proposal in contrast to the USAMRMC format of organizing some materials critical for the review as addenda.

LSRO and the expert panel completed all tasks requested by the sponsor. LSRO anticipates that these recommendations will serve the sponsor and if implemented, that resuscitation science research will advance and eventually lead the sponsor to one or more AFRRF products that will substantially improve resuscitative care in combat and save the lives of U.S. soldiers and marines.

Table V-1 Principal recommendations of the AFRRF expert panel.*

		Recommendation	Rationale
The framework for reviewing proposals			
Indication for treatment	Define the specific indication that the proposed product will treat by listing clinical conditions of the targeted patient population	Such characterization would limit the scope of treatment and refine the inclusion criteria to blood volume expanders and individual pharmacologic agents that could be administered in concert with conventional hypotensive resuscitation before and/or after administration of resuscitation fluid, and contribute to the development of relevant experimental models	
Product requirements	Define minimal and optimal product performance goals (<i>i.e.</i> , requirements) and prioritize the product performance goals	Criteria for product performance are needed to evaluate military relevance	
Product categories	Distinguish between two product categories for submission, encouraging investigation of novel fluids for blood volume expansion as well as emphasizing the need for novel pharmacologic agents that can be used with or without various resuscitation fluids	Novel blood volume expanders that can partially or fully replace blood volume in combatants and that can be titrated to a physiological endpoint are desirable. One or more pharmacologic agents may be needed in addition to the blood volume expander to improve survival rates	
Funding cycle	Limit budget periods for specific AFRRF project proposals to a maximum of two years for preclinical studies and a maximum of three years for clinical studies with the potential for additional funds if the project is on track and successful	Imposing these time limits on funding cycles strengthens the product development process by advancing successful products and projects and halting unsuccessful ones sooner rather than later	

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Table V-1 (continued).

		Recommendation	Rationale
Communication			
Communication	Consider developing a website to provide information to those interested in applying for AFRRF awards	Improving access to proposal instructions, forms, and other relevant information will streamline and simplify the proposal submission process and help the sponsor obtain relevant and high quality proposals	
Peer-review	Rely on a multidisciplinary standing committee of experts to evaluate future preproposals. Additional review panels or <i>ad hoc</i> reviewers may be needed for review of full proposals. Military experts should serve as consultants to the committee and review panels	A multidisciplinary standing committee will provide sufficient breadth and depth of knowledge and experience to identify leading candidates that have scientific merit and military relevance	
Methodologies			
Methodologies	Organize a meeting of experts to identify improvements in methodologies for measuring indications, for monitoring and for measuring outcomes of resuscitative care	Improving methods for obtaining more accurate and precise measures will advance resuscitation science investigations and clinical practice	
Future proposal processes and forms			
Format	Format a standardized packet for use by those submitting future AFRRF preproposals and proposals	Defined formats for completion encourage submission of sufficient relevant information, organized to be efficiently reviewed	
Page limits	Impose stringent page limits for preproposals and proposals	Page limits help to minimize reviewer-burden and sets a consistent standard for all submissions	
Product characterization and relevance	Require that future preproposals and proposals contain sections for product identification and characterization, a commercialization plan, and a discussion of the military relevance of the product	Specifying a requirement to include such information assists in obtaining the materials necessary for the reviewers to evaluate military relevance and commercial viability	

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Table V-1.(continued).

Experimental models and clinical studies		Recommendation	Rationale
Preclinical model		Preclinical AFRRF studies should include non-anesthetized models to study hemorrhage alone and an anesthetized model to study uncontrolled hemorrhage plus trauma in two species of large animals with hypotensive resuscitation during prolonged periods	Use of conscious animals minimizes artifacts resulting from anesthesia, which can obscure hemodynamic responses to treatment. The recommended models represent similar physiological responses to the far-forward treatment interval in which the wounded combatant awaits evacuation to surgical care
Preclinical end points		Preclinical studies should measure short-term survival during conditions that simulate delayed evacuation to surgical care, and should measure end organ damage and long-term survival	The recommended endpoints indicate functionality of AFRRF products under combat conditions
Human model		The best surrogate model for treatment of combat inflicted hemorrhage is the use of AFRRF products by civilian emergency medical technicians to treat extensive blunt trauma	Extensive blunt trauma, such as extremity injuries resulting from motor vehicle accidents, represents the greatest frequency of civilian traumatic injuries that are relevant to combat-inflicted hemorrhage occurring in areas of the United States where most medical research for FDA licensure is conducted
Clinical end points		Clinical studies should measure coagulation profile, neurological status, end organ failure, and survival to 28 days and to 60 days	The coagulation system is prone to dilution and other effects from resuscitation. Neurological measures are important to determine the severity of shock and/or identify concurrent neurotrauma. A successful treatment would achieve and maintain optimal organ function.
Military indication		Leading candidates should be validated under battlefield conditions	Civilian studies will not represent the varied situations and experiences of wounded combatants

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Table V-1.(continued).

Future peer-reviewers		Recommendation	Rationale
Independence		Reviewers should excuse themselves from reviewing and ranking preproposals and proposals from their institution, by researchers they have collaborated with during the past three years, and by researchers with whom they have/had a mentor relationship	Independence is necessary to avoid potential conflict of interest
Expertise		Reviewers should conduct the initial review of preproposals and proposals that fall within their area of expertise and research interests	Expert reviewers provide sufficient breadth and depth of knowledge and experience to identify leading candidates that have scientific merit and military relevance
Resources		The initial review form and scoring methods developed by the AFRRF expert panel are available resources to formulate methods pertinent to the future reviews	Such resources help to expedite future reviews
Individual scoring		Reviewers should rank preproposals and proposals by individual scores rather than by direct comparisons among submissions	Holding all preproposals to the same standard of evidence will avoid the situation of comparing one preproposal or proposal for which some expert panel members were excused for potential conflict of interest (and not privy to deliberation) with another preproposal or proposal for which the expert panel members were not excused
Ranking subgroup	within	Sort preproposals or proposals into preclinical and clinical categories for review purposes	Preclinical studies could be better controlled and could have greater breadth of experimental procedures and measures than clinical studies yet may be more speculative than products ready for clinical trial

*AFRRF: Advanced first-responder resuscitation fluid; FDA: U.S. Food and Drug Administration.

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VII. STUDY PARTICIPANTS

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APPENDIX A. INDIVIDUALS AND ORGANIZATIONS

A.1 AD HOC EXPERT PANEL MEMBERS

Bradley A. Boucher, Pharm.D., F.C.C.P., F.C.C.M., B.C.P.S., received a B.S. (1979) and Pharm.D. (1983) from the University of Minnesota, and completed the American Society of Health-System Pharmacists Critical Care Fellowship at the University of Kentucky (1984). He is certified as a Pharmacotherapy Specialist (Board of Pharmaceutical Specialties, 1992) and is a fellow of the American College of Clinical Pharmacy (1998) and the Society of Critical Care Medicine (2000). Dr. Boucher is a clinical pharmacist in critical care at the Regional Medical Center at Memphis. He is also Professor of Clinical Pharmacy and Associate Professor of Neurosurgery at the University of Tennessee, Memphis. His research interests include head trauma and the medical management of critically ill trauma patients. Dr. Boucher is Past-President of the American College of Clinical Pharmacy (2001-2002), and since 2000, has served on the editorial board of the *Journal of Informed Pharmacotherapy and Critical Care Medicine*.

Kenneth E. Burhop, Ph.D., received a B.A. in zoology from the University of Wisconsin-Milwaukee (1976), and an M.S. (1979) and Ph.D. (1984) in veterinary science from the University of Wisconsin-Madison. He also completed a National Institutes of Health Pulmonary Research Postdoctoral Fellowship in the Department of Physiology at Albany Medical College (1986). Dr. Burhop is currently Vice President of Project Management, Research and Development, and Medication Delivery at Baxter Healthcare Corporation, Deerfield, IL. He has over 17 years experience in product research and development within an industrial setting, and was formerly Vice President, Research and Development, Hemoglobin Therapeutics Division, Baxter Healthcare Corporation, Boulder, CO. His research interests include preclinical safety and efficacy assessment of biotechnology products, hemoglobin-based blood substitutes, and virtual research and development networks. He holds more than six U.S. and foreign patents. Dr. Burhop is a member of several professional organizations, including the American Physiological Society, American Federation for Clinical Research, the Shock Society, the International Society for Oxygen Transport, and the Society of Critical Care Medicine.

James W. Holcroft, M.D., (Chair) received a B.S. in electrical engineering from the Massachusetts Institute of Technology (1963) and an M.D. from Case Western Reserve University (1969). Dr. Holcroft was certified by the American Board of Surgery (1977), and received a Certificate of Special Qualifications in General Vascular Surgery (1986) and a Certificate of Added Qualifications in Surgical Critical Care (1987). He is a Distinguished Fellow of the Society for Vascular Surgery (1984). Dr. Holcroft is Director of the Surgical Intensive Care Unit at the University of California, Davis Medical Center. He is also Professor of Surgery at the Davis School of Medicine, Sacramento, CA. His major professional interests are cardiovascular physiology and monitoring, fluid resuscitation, and scoring systems for predicting outcomes in critical illness. He is co-inventor on a patent for the use of hypertonic solutions in conjunction with colloid for resuscitation of acutely injured patients. Dr. Holcroft served in the U.S. Army Medical Corps Reserves from 1977 to 1993. He is a member of numerous professional organizations and has held leadership positions in the Shock Society (2001-2002), the American College of Surgeons (1988-1989), the Association for Academic Surgery (1983-1984), and the American Association for the Surgery of Trauma (1997-1998). He serves on the editorial boards of *Scientific American*, *Shock®*, and *Surgery* and was a consultant to an extramural review committee at the Institute of Medicine (1998-1999).

Jureta W. Horton, Ph.D., received a B.A. from our Lady of the Lake University (1962) and a Ph.D. from the University of Texas Health Science Center (1981). She is currently a Professor in the Department of Surgery and Director of the Burn, Trauma and Critical Research and Training Programs at the University of Texas Southwestern Medical Center, Dallas. Her research interests include signaling through the Toll/IL-1 pathway to regulate myocardial inflammatory cytokine synthesis and myocardial function, mitochondrial calcium handling and myocyte replication. She is a member of several professional organizations including the American Association for the Surgery of Trauma, the American Burn Association, the Critical Care Medicine Society, and is Past-President of the Shock Society (2000-2001). She serves on the editorial boards of the *Journal of Burn Care & Rehabilitation* (2004) and *Shock®* (since 1992). Dr. Horton served as a reviewer on the National Merit Review Board for the Veterans Administration (1991-1997) was a standing member of the SAT/NIH Study Section (1993-1997) and is currently Chairman of the Research Advisory Board for the Shrine Hospital System. She has held numerous peer-review positions including serving on the National Academy of Sciences, Institute of Medicine Committee on Fluid Resuscitation for Combat Casualties (1998).

John A. Kellum, M.D., F.A.C.P., F.A.C.C.P., F.C.C.M., received a B.A. in pre-med and psychology from the University of Toledo (1984) and an M.D. from the Medical College of Ohio at Toledo (1988). He is a fellow of the American College of Chest Physicians (1996), the American College of Physicians (1998), and the Society of Critical Care Medicine (1999). He was certified by the American Board of Internal Medicine in internal medicine (1991) and in critical care medicine (1996). Dr. Kellum is currently an intensivist in the Department of Critical Care Medicine at the University of Pittsburgh Medical Center and is Associate Professor of Critical Care Medicine at the University of Pittsburgh School of Medicine. He also co-directs the MANTRA (Mechanisms and Novel Therapies for Resuscitation and Acute illness) laboratory and is Director of the molecular core for the CRISMA (Clinical Research Investigation and Systems Modeling of Acute illness) laboratory at the University of Pittsburgh. His research interests include inflammatory markers of sepsis, multi-organ failure, renal replacement therapy, and clinical epidemiology. Funding for his research has been provided by the National Institutes of Health, the Health Resources and Services Administration of the U.S. Department of Health and Human Services, Abbott Labs, Eli Lilly and Co., and Glaxo-Smith-Kline. Dr. Kellum is a member of the group STORMACT (Strategies to Reduce Military and Civilian Blood Transfusions). He is also a member of several professional societies, including the Society of Critical Care Medicine and has served as a peer-reviewer for the National Institute of Diabetes and Digestive and Kidney Diseases and the National Heart, Lung, and Blood Institute.

Donald S. Prough, M.D., received a B.A. in English from Lafayette College (1969) and an M.D. from Milton S. Hershey Medical Center. He is a diplomate of the American Board of Anesthesiology (1977) and holds a Certificate of Special Competency in Critical Care (1986). Dr. Prough is currently Professor and Chair of the Department of Anesthesiology at the University of Texas Medical Branch, School of Medicine, Galveston, TX and also serves as Assistant Director for Clinical Research of the Center for Biomedical Engineering. His academic interests include traumatic brain injury, cerebrovascular physiology, kinetics of intravenous fluids, electrolyte abnormalities, hemorrhagic shock and sepsis. He has received grants from the Office of Naval Research, the U.S. Army Medical Research and Materiel Command, and the National Institutes of Health. Dr. Prough holds a patent on optoacoustic monitoring of blood oxygenation. Formerly, he was Medical Director of the Regional Cerebral Blood Flow Laboratory, Bowman Gray School of Medicine, Wake Forest University, Chapel Hill, NC (1985-1992). Dr. Prough is a retired Captain U.S. Naval Reserve, Medical Corps, having served in active duty (1970-1980) and in the active reserves (1985 to 2000). He was elected President of the Association of University Anesthesiologists (2003-2004), and of the American Society of Critical Care Anesthesiologists (1998-1999), and is a Board of Trustees member for the International Anesthesia Research Society. He has served on numerous medical committees, including the Anesthesiology and Respiratory Therapy Devices Panel of the Food and Drug Administration's Medical Devices Advisory Committee (Chair, 2002-2003). Dr. Prough also serves on the editorial boards of several journals, including *Critical Care Medicine* and *Anesthesiology*. In 2001, the American Society of Critical Care Anesthesiologists honored Dr.

Prough with a Lifetime Achievement Award and in 1997 he received the Distinguished Investigator Award from the American College of Critical Care Medicine.

Ori D. Rotstein, M.D., F.R.C.S.C., F.A.C.S., received an M.D. (1977) and a M.S. (1982) from the University of Toronto, Ontario, Canada. He is a Fellow of the Royal College of Physicians and Surgeons of Canada (1982) and of the American College of Surgeons (1991). Dr. Rotstein is currently Professor of Surgery and Director of the Institute of Medical Science at the University of Toronto, and is Surgeon-in-Chief of St. Michael's Hospital in Toronto. His research focuses on the cellular and molecular aspects of organ injury following shock, trauma, and surgical infection. Funding for some of his work has been provided by the Canadian Institute of Health Research, Plasma Protein Therapeutics, and the Canadian Red Cross. He holds patents on a method for preventing necrosis and apoptosis and for an anti-inflammatory and anti-pyretic method. Dr. Rotstein has held leadership positions for numerous medical and scientific committees, including a position as Executive Director, Surgical Infection Society Foundation for Research and Education. He serves on several editorial boards including *Shock* (1993-present) and the *Journal of Surgical Research* (1996-present). He has also served as a consultant for Merck Pharmaceuticals, Wyeth Pharmaceuticals, Bayer Pharmaceuticals, and Cubist Pharmaceutical. Dr. Rotstein has held numerous peer-review positions including serving as a member of the Grant Review Panel, Microbiology and Infectious Disease, Medical Research Council of Canada.

William J. Sibbald, M.D., M.P.H., F.R.C.P.C., F.C.C.H.S.E., received an M.D. from the University of Western Ontario (1970) and a Masters in Public Health (MPH) from the Medical College of Wisconsin (2003). He is a Fellow of the Canadian College of Health Service Executives (2000) and both the Royal College of Physicians/Surgeons of Canada (1975) and of Edinburgh (2002). Dr. Sibbald is currently Professor of Medicine, Critical Care at the University of Toronto, Ontario, Canada and Physician-in-Chief of the Department of Medicine at Sunnybrook and Women's College Health Sciences Centre in Toronto. His research focuses on health services, the biology of sepsis and the systemic inflammatory response syndrome in critically ill patients. He has published several studies on the impact of different fluid solutions and blood substitutes on the progression of illness in animal models of shock and sepsis. Dr. Sibbald is Past-President of the Canadian Critical Care Society (1984-1986). He is Editor-in-Chief of the *Journal of Critical Care* and serves on several other editorial and advisory boards, including that of *Sepsis*, *Critical Care*, and *Critical Care Medicine*. Dr. Sibbald received the Distinguished Investigator Award of the American College of Critical Care Medicine in 1998 and a Distinguished Service Award from the Society of Critical Care Medicine (USA) in 2004. Dr. Sibbald holds peer-reviewed grants from the Canadian Institute of Health Research, the National Institutes of Health, the Heart and Stroke Foundation of Ontario, and other granting agencies.

A.2 Life Sciences Research Office Staff

Michael Falk, Ph.D., is the Director of the Life Sciences Research Office Inc. (LSRO). He received his Ph.D. in biochemistry from Cornell University and completed postdoctoral training at Harvard Medical School. He was employed in various capacities at the Naval Medical Research Institute, Bethesda, MD supervising as many as 80 senior level scientists. As Principal Investigator he was a key member of the Scientific Advisory Board and Acting Director for the institute. He was also the Director of the Wound Repair Program and Director of Biochemistry and Cell Biology. As Director, he rescued the Septic Shock Research Program by cutting inefficiencies and increasing productivity in terms of grant funding and publication production. He managed peer reviews and subject review panels in infectious diseases, environmental sciences, military medicine, and other health-related fields for the National Science Foundation, Medical Research Council of Canada, and the Office of Naval Research. As Director of LSRO, Dr. Falk manages the evaluation of biomedical information and scientific opinion for regulatory and policy makers in both the public and private sectors. He has written seminal white papers on infant nutrition, food labeling, food safety, and military dental research, and has organized two international conferences.

Robin S. Feldman, B.S., M.B.A., is the Literature Specialist at LSRO. She is an information specialist with experience in the electronic acquisition, analysis, and management of scientific, business, and regulatory information. Ms. Feldman obtained her B.S. from George Washington University, Washington, D.C., with a major in zoology and an M.B.A. with a concentration in science and technology from the University of Maryland at College Park. Previously, she worked as Biomedical Research Assistant at Consultants in Toxicology, Risk Assessment and Product Safety, where she obtained and researched scientific literature for private and governmental clients. At the National Alliance for the Mentally Ill, she designed and implemented a document management and retrieval system for the Biological Psychiatry Branch of the National Institute of Mental Health and served as Managing Editor of *Bipolar Network News*, a newsletter for the Stanley Foundation Bipolar Network. At Howard Hughes Medical Institute, she oversaw the implementation of the Predoctoral Fellowship in Biological Sciences program. While serving as Science Information Specialist at the Distilled Spirits Council of the United States, she managed the installation of a local area network and participated in the development and maintenance of an electronic research database for the beverage alcohol industry. As a Report Coordinator at Microbiological Associates, Inc. she conducted statistical analyses and prepared technical reports about toxicology studies using animal models. She also served as Data Management Administrator for the National Toxicology Program's sponsored studies. Currently, Ms. Feldman maintains LSRO's library, responds to requests for reports, and assists LSRO's scientists in discovering, obtaining, compiling, and documenting the scientific literature required to prepare reports for sponsors.

Karin French, B.S. received a B.S. degree in Animal Science and a B.S. degree in Cell and Molecular Biology and Genetics from the University of Maryland, College Park. In addition, she earned a College Park Scholars Certificate in 'Science, Technology, and Society'. She joined Life Sciences Research Office in Bethesda, Maryland in November 2003 as an Associate Staff Scientist. She previously worked in dairy nutrition at the University of Maryland, helping dairy farmers use milk urea nitrogen (MUN) to evaluate herd protein nutrition. She helped design and complete studies to compare and evaluate the MUN analysis techniques used in the National Dairy Herd Improvement Association laboratories.

Rebecca Johnson, Ph.D., received her B.A. in anthropology from Wesleyan University, and her Ph.D. in anthropology with a concentration in archaeology from the University of Iowa. Her dissertation research examined dietary change between two Native American villages in southeastern Iowa, dated to 1950 and 1600 B.P., by looking at fatty acid residues extracted from pottery. Dr. Johnson has performed fieldwork across the Mid-Atlantic and Upper Midwest, as well as South Carolina, Great Britain, and Poland. Dr. Johnson joined LSRO in September 2004 as Assistant Information Specialist. At LSRO, she assists in maintaining the library, responding to requests for reports, and organizing the scientific literature required by staff scientists for sponsored projects. Previously, Dr. Johnson developed and maintained statewide archaeological databases for Iowa's Office of the State Archaeologist.

Catherine J. Klein, Ph.D., R.D., C.N.S.D., is a Senior Staff Scientist at LSRO. She graduated *magna cum laude* from the Department of Human Nutrition and Food Science at the University of Maryland at College Park, where she also obtained her M.S. and Ph.D. in nutrition. She completed internships in the Pre-Professional Practice Program in Dietetics at the University of Maryland Medical System (UMMS), Baltimore, MD, the V.A. Kleinfeld Summer Internship Program at the Food and Drug Law Institute, Washington, D.C., Dannon's Nutrition Leadership Institute, Wye River, MD, and most recently, the American Dietetic Association's Leadership Institute, St. Petersburg, FL. At UMMS, she developed system-wide guidelines for nutrition assessment, documentation, and continuity of care. As Clinical Coordinator of Research in the Division of Critical Care Medicine at the University of Maryland R Adams Cowley Shock Trauma Center, Baltimore, MD, she developed, initiated, and administered research projects focused on nutrition issues in critical care. She established a multidisciplinary nutrition task force, which resulted in improvements in clinical practice standards. She is the primary author on nine peer-reviewed publications, including a book chapter, and has lectured or presented at over 26 professional meetings. Dr. Klein received the Pelczar Award for Excellence in Graduate Study from the University of Maryland, Graduate School and Sigma Xi, and the Dr. E.V. McCollum Award from the Maryland Dietetic Association. Her professional contributions include serving on the Advisory Board of the University of Maryland Dietetics Program and as editor for the Maryland Dietetic Association.

A.3 Invited Presenters

A.3.1 Presentations to panel on January 10, 2005

“Overview of Resuscitation Fluid Research Program” and “Sponsor Tasks Panel”

COL James L. Atkins, M.D., Ph.D., F.A.C.P.

Division Military Casualty Research

Walter Reed Army Institute of Research

Silver Spring, MD

“Standard of Care for Resuscitation Fluid in Combat”

COL David G. Burris, M.D., F.A.C.S., D.M.C.C.

Norman M. Rich Department of Surgery

Uniformed Services University of the Health Sciences

Bethesda, MD

“Milestones and Metrics in Resuscitation Fluid R&D”

Charles E. Wade, Ph.D.

U.S. Army Institute for Surgical Research

Fort Sam Houston, San Antonio, TX

“The Need for Prioritizing Criteria”

William H. Howell, M.S.

U.S. Army Medical Research and Materiel Command

Fort Detrick, MD

A.3.2 Biosketches

COL James L. Atkins, M.D., Ph.D., F.A.C.P., received an A.B. degree from the University of Notre Dame (1969), a M.D. from the University of Maryland School of Medicine (1975), and a Ph.D. from the University of Maryland, Baltimore (1978). He was certified by the American Board of Internal Medicine (1978) with a subspecialty in Nephrology (1986). He is a Fellow of the American College of Physicians. Since 1982, he has been in active duty in the United States Army, with a rank of Colonel since 1992. COL Atkins is currently Director of the Division of Military Casualty Research at the Walter Reed Army Institute of Research (WRAIR), Silver Spring, MD and is the Program Area Manager for Resuscitation Research in the Army Combat Casualty Care Program, which is part of the Medical Research and Materiel Command (MRMC) at Ft. Detrick, MD. This program oversees resuscitation studies conducted at WRAIR and the Institute of Surgical Research in Texas. It also awards and oversees some extramural grants. He is also Associate Professor of Medicine in the F. Edward Herbert School of Medicine, Uniformed Services University of Health Sciences, Bethesda, MD. COL Atkins was elected to the Order of Military Medical Merit (2003) for his significant contributions to the army medical system and was presented with the Army Meritorious Service Medal (2004) for his “management and conduct of resuscitation research.” He served as the MRMC representative on numerous committees of the National Institutes of Health initiative for the Post-Resuscitative and Initial Utility in Life Saving Efforts (PULSE) program. In 2003, he was recognized at the first American Heart Association Resuscitation Science Symposium (ReSS) for “Outstanding Leadership in Resuscitation Research.” COL Atkins has held numerous peer-review positions for the National Kidney Foundation, including Chairman, Grant Review Committee, Washington Chapter (2001-2003).

COL David G. Burris, M.D., F.A.C.S., D.M.C.C., earned a B.S. degree in chemistry from Arizona State University in Tempe (1978) and a M.D. from the Uniformed Services University of the Health Sciences (USUHS), Bethesda, MD (1982). COL Burris is certified by the American Board of Surgery in general surgery and critical care and has a diploma in the Medical Care of Catastrophes from the Society of Apothecaries of London (1995). Since 1978, he has been in active duty in the United States Army, with a rank of Colonel since 2000. He is Professor and Interim Chairman of the Norman M. Rich Department of Surgery of USUHS. Previously, he held positions at USUHS as Chief of the Division of Surgical Research (1994-2001) and Deputy Chairman, Department of Surgery (2001-2002). Since 1994, COL Burris has also held a clinical appointment as attending surgeon in general surgery and surgical critical care at Walter Reed Army Medical Center, Washington, DC. In 2003, COL Burris served as Senior Surgeon and Deputy Commander of Clinical Services of the 912th Forward Surgical Team in Baghdad, Iraq. Among other military awards, he was presented with the Defense Meritorious Service Medal (1999), the Global War on Terrorism Service Medal (2003), and the Global War on Terrorism Expeditionary Medal (2003). In 1999, he was honored with the Baron Dominique Jean Larrey Military Surgeon's Award for Excellence. His research in combat casualty care includes resuscitation fluids, blood substitutes, and hemostatic agents. Currently, he is the American Association for the Surgery of Trauma's representative to the National Association for Biomedical Research, the Military Region Chief for the American College of Surgeons' Committee on Trauma, and is a member of numerous other professional organizations.

William H. Howell, M.S., received a B.A. in history from Furman University in Greenville, SC (1974), a M.S. in logistics management through the Logistics Executive Development Course program, Florida Institute of Technology, Ft. Lee, Virginia (1986), and a M.S. in National Resource Strategy from the Industrial College of the Armed Forces (1996). Mr. Howell has earned Level 3 Certification in military acquisition. He is Deputy for Acquisition for the U.S. Army Medical Research and Materiel Command, Fort Detrick, MD, having held positions of increasing responsibility in military logistics and acquisitions since 1978. He was commissioned in the U.S. Army Ordnance Corps in 1974 and served through 1978.

Charles E. Wade, Ph.D., received an A.B. in physical education from Occidental College, Los Angeles, CA (1972), a M.A. in physical education from the University of California, Davis (1975), and a Ph.D. in biomedical sciences and physiology from the University of Hawaii, School of Medicine (1979). He conducted his post-doctoral work in physiology at the University of California, San Francisco (1979-1981). Dr. Wade is a fellow of the American College of Sports Medicine. Currently, he is a research physiologist with the U.S. Army Institute for Surgical Research, Fort Sam Houston, San Antonio, TX and has held a position as Adjunct Professor in the Department of Neurobiology, Physiology, and Behavior at the University of California, Davis since 1996. From 1994-2004, Dr. Wade was Senior Staff Scientist in the Life Sciences Division, Ames Research Center of the National Aeronautics and Space Administration (NASA), Moffett Field, CA, where he also served as Acting Division Chief from 2002-2003. His research interests include neuroendocrine modulation in humans and in animal models and the role hormones play in adaptation to altered environmental conditions, especially the conditions of spaceflight. In addition, he has published numerous studies of resuscitation using hypertonic saline and dextran solutions. Dr. Wade has served on several scientific advisory committees for the Letterman Army Medical Center, the NASA Ames Research Center, and the National Research Council. His professional affiliations include membership in the American Physiological Society, the American Society for Gravitational and Space Biology, the Society for Experimental Medicine and Biology, and the Shock Society. Dr. Wade is a member of the editorial board of the *American Journal of Physiology*. He has received numerous NASA service awards, including the NASA Exceptional Service Medal (2003), was honored with the Department of Army Research and Development Award (1989), and was named the Presidio of San Francisco Employee of the Year in the Sciences (1984).

A.4 Life Sciences Research Office Board of Directors (2005)

Chair: Taffy J. Williams, Ph.D.
IMCOR Pharmaceuticals
Montgomeryville, PA

Vice Chair: Terry Quill, M.S., J.D.
International Society for Regulatory Toxicology and Pharmacology
Washington, DC

Treasurer: Arnold Kahn, Ph.D.
University of California-San Francisco
San Francisco, CA

Past Chair: Salvatore J. Enna, Ph.D.
University of Kansas Medical Center
Kansas City, KS

Secretary: Michael C. Falk, Ph.D.
Life Sciences Research Office
Bethesda, MD

Directors: Eileen Kennedy, Ph.D.
Friedman School
Boston, MA

William MacLean, Jr., M.D.
Consultant
Columbus, OH

Thomas Stagnaro, B.S.
Americas Biotech Distributor
Riva, MD

Jacob J. Steinberg, Ph.D.
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, NY

APPENDIX B. BROAD AGENCY ANNOUNCEMENT

FedGrants

Federal Funding Opportunities



Candidate Technologies for Advanced First-Responder Resuscitation Fluid (AFRRF)

General Information

Document Type:	Grants Notice
Funding Opportunity Number:	W81XWY-BAA-AFRRF
Posted Date:	Aug 03, 2004
Original Due Date for Applications:	Sep 07, 2004
	Due by 2:00 PM, September 7, 2004
Current Due Date for Applications:	Sep 07, 2004
	Due by 2:00 PM, September 7, 2004
Archive Date:	Nov 06, 2004
Funding Instrument Type:	Cooperative Agreement Grant Other
Category of Funding Activity:	Science and Technology and other Research and Development
Expected Number of Awards:	25
Estimated Total Program Funding:	\$4,000,000.00
Award Ceiling:	\$1,000,000.00
Award Floor:	None
CFDA Number:	12.910 -- Research and Technology Development
Cost Sharing or Matching Requirement:	No

Eligible Applicants

Unrestricted (i.e., open to any type of entity above), subject to any clarification in text field entitled "Additional Information on Eligibility"

Agency Name

US Army Medical Research Acquisition Activity, ATTN: MCMR-AAA, 820 Chandler Street, Frederick, MD 21702-5014

Description

Supplement to the U.S. Army Medical Research Materiel Command Broad Agency Announcement (BAA) 04-1: Candidate technologies for advanced first-responder resuscitation fluid (AFRRF)

SUBJECT: The purpose of this announcement is to request pre-proposals regarding candidate

technologies/products for fluid resuscitation that can be used by first responders and combat medics to resuscitate wounded military personnel on the battlefield.

DESCRIPTION: The U.S. Army Medical Research and Materiel Command (Fort Detrick, MD), in cooperation with the Office of Naval Research (Arlington, VA), seeks research on candidate technologies-products that can potentially be applied to development of a resuscitation fluid(s) or resuscitation fluid adjunct(s) that can be readily and easily administered by first responders and combat medics on the battlefield. By 2020, or earlier, the Army, the Navy, and the Department of Defense (DoD) seek to significantly reduce the number of casualties who are killed-in-action (KIA, expire before reaching a medical treatment facility) by providing improved, more effective fluid resuscitation earlier after the wounding event. A secondary goal is to substantially mitigate post-wounding and post-resuscitation morbidity.

Respondents are encouraged to provide information about fluid resuscitation technologies-products that potentially can be or have been demonstrated to be effective in treating blood loss and shock, preventing complications, and improving chances for survival.

Responses will be compiled by the Life Sciences Research Office (LSRO) in consultation with an Expert Panel, which has been engaged to conduct an independent review and prioritize candidate technologies/products. Full proposals will be requested for technologies deemed to be of interest and applicable to our goals.

FUNDING AVAILABLE FOR AWARD: Technologies selected for collaboration and continued development by the DoD will be eligible for extramural (or any combination of extramural and intramural collaboration) awards of \$100K to \$500K for pre-clinical studies and up to \$1M for early (Phase 1 or Phase 2) clinical studies. Total available funding for all awards is approximately \$4 million per year until 2010. Awards may be in the form of assistance agreements (grants or cooperative agreements) or contracts.

PRODUCT REQUIREMENTS: The military is open to alternatives to standard solutions that can be used to treat volume deficits resulting from blood loss in far forward deployment areas. Hence, product requirements are based on logistical considerations of transport, storage, and utilization in combat field conditions as well as medical considerations. Products proposed in response to this request must meet one or more of these functional requirements:

- * Fluid conservative treatment with hypotensive end-points
- * Stable for prolonged periods at typical battlefield temperatures (less than or equal to 130 degrees Fahrenheit, including less than 32 degrees Fahrenheit)
- * Provides supplemental oxygen-carrying capacity
- * Mitigates or negates post-shock, post-resuscitation syndromes
- * Compatible with blood products
- * Easily and quickly administered by first-responder-medical personnel with limited training
- * No mental or physical post-resuscitation impairment specific to the treatment

To the extent that simplifying assumptions about these product requirements are needed, respondents are encouraged to make and document such assumptions in their response.

RESPONSE OUTLINE: In lieu of a preproposal, this announcement requires responses that must contain the following information and data to the extent that they are available:

1. Product description: Briefly describe the candidate technology/product and whether the product is approved for other uses.
2. Data: Summarize the supporting *in vivo*, pre-clinical and clinical data that validate the benefits/utility of this product. Describe the mode of action. Please comment on any safety evaluations that have been conducted and additional studies underway or planned for the near-future.
3. Implementation: Discuss schedule considerations for how soon the product would be ready

for human clinical trials and whether Phase III funding is available.

4. Other: Provide any other materials and discussion you deem appropriate, including your willingness to present information to the Expert Panel in the future.

Submissions will be evaluated in accordance with the criteria outlined in the Broad Agency Announcement 04-1 for at www.usamraa.army.mil under the BAA button.

Point of contact for inquiries about response content and the LSRO project:

Dr. Catherine Klein
(301) 634-7032
kleinc@LSRO.org
www.LSRO.org

SUBMISSION OF INFORMATION: Responses are not limited by country of origin but must be in the English language. Only information contained in the first 5 pages of the response will be considered. LSRO endeavors to make the review process as public as possible; hence, non-proprietary information is preferred. However, LSRO has made provisions to handle confidential and proprietary information so that each page of response marked 'Proprietary' and/or 'Confidential' will be handled accordingly. Please provide the name and contact information of an individual who could respond to requests by LSRO for additional information.

Submissions in response to this announcement must be sent to the following address and must be received not later than 2 PM, 7 September 2004. Submissions should consist of one hard copy and electronic files on a CD compatible at least with Windows 2000 or XP operating systems. Submissions received after this date will not be guaranteed a full review by LSRO.

Mail or courier submissions to:

USAMRAA
ATTN: W81XWY-BAA-AFRRF
820 Chandler Street
Fort Detrick, MD 21702-5014

Link	to	Full	Announcement:
http://www.fedgrants.gov/Applicants/USA/USAMRAA/DAMD17/W81XWY-BAA-AFRRF/			
Candidate Technologies for Advanced First-Responder Resuscitation Fluid (AFRRF)			
If you have difficulty accessing the full announcement electronically, please contact:			
Cheryl Miles, 301-619-7148, cheryl.miles@det.amedd.army.mil Cheryl Miles			

APPENDIX C. LETTERS TO THE SPONSOR

C.1 Notice of Excluded Preproposals



LIFE SCIENCES RESEARCH OFFICE

9650 Rockville Pike • Bethesda, Maryland 20814-3998
Telephone (301) 634-7030 • Fax (301) 634-7876
Email: LSRO@LSRO.ORG • Web: WWW.LSRO.ORG

February 4, 2005

Michael Falk, Ph.D.
Executive Director

COL Robert H. Vandre, DDS
Director U.S. Army Combat Casualty Care Research Program
U.S. Medical Research and Materiel Command
722 Doughton Street
Fort Detrick, MD 21702-5012

Dear Dr. Vandre:

This letter is to inform you that the Life Sciences Research Office (LSRO) has identified six pre-proposals that do not meet inclusion criteria and are therefore excluded from further review by the Advanced First-Responder Resuscitation Fluids (AFRRF) Expert Panel. We are notifying you in advance of our full report so that the army can proceed expeditiously to inform these researchers of the status of their pre-proposals.

Five (015, 016, 026, 038, 041) of the six pre-proposals were excluded for proposing to study a device(s), rather than a resuscitation fluid or component of resuscitation fluid. The sixth pre-proposal (008) concerned the development of a prognostic early marker of organ failure and did not propose to study resuscitation fluid. If you have any questions about the exclusion of these pre-proposals, please contact me.

I have attached a table containing a brief description of each pre-proposal. Copies of the full pre-proposals will be sent to you should you request them. Pre-proposal 015 is confidential.

It is our understanding that all letters of response to submitters must go through Ms. Cheryl R. Miles, as she is the contracting officer of record for the AFRRF award (U.S. Army Medical Research Acquisition Activity, Fort Detrick, MD). Pending your response, we can prepare letters to send to these researchers. We will forward the letters to Ms. Mile's for signature.

You have engaged us in an interesting and challenging project and we look forward to the remaining work ahead. I believe the final report will have great value to the Sponsor and to the medical-trauma community at large.

Regards,

A handwritten signature in black ink, appearing to read "Catherine J. Klein".

Catherine J. Klein, PhD
Senior Staff Scientist and Project Leader
Life Sciences Research Office
(301) 634-7032
kleinc@LSRO.org

Enclosure: Table of six excluded AFRRF pre-proposals

C.2 Transmittal of Interim Provisional Results



LIFE SCIENCES RESEARCH OFFICE

9650 Rockville Pike • Bethesda, Maryland 20814-3998
Telephone (301) 634-7030 • Fax (301) 634-7876
Email: LSRO@LSRO.ORG • Web: www.LSRO.ORG

Michael Falk, Ph.D.
Executive Director

May 23, 2005

COL Robert H. Vandre, DDS
Director U.S. Army Combat Casualty Care Research Program
U.S. Medical Research and Materiel Command
504 Scott Street
ATTN: MCMR-ZB-DRC
Fort Detrick, MD 21702-5012

Dear Dr. Vandre:

This letter is to inform you that the Advanced First-Responder Resuscitation Fluids (AFRRF) Expert Panel has identified seven leading candidates among the 59 preproposals considered. We are notifying you of the provisional results in advance of our full report so that the army can make preparations to begin their own evaluations.

The information in the accompanying tables and files reflects the current priority of the expert panel, but the Life Sciences Research Office, Inc. reserves the right to make changes, until the report is finalized.

The expert panel's intention in scoring preproposals and making their selection of leading candidates was to enable the sponsor to identify strategies having the best potential in the not too distant future to save soldier's lives on the battlefield and reduce downstream morbidity and mortality. As described in the report text, based on the scores assigned for military relevance and scientific merit by two initial reviewers, preproposals were either advanced to full panel scoring or were categorized as having insufficient merit for funding. Preproposals that were advanced and scored by the full panel were rank ordered by the sum of the military and scientific scores; the lower the score, the higher the rank of the preproposal (i.e., range one (best merit) to five (least merit)).

Attached you will find confidential provisional results in an Excel file containing three spreadsheets: (1) all 10 clinical preproposals, (2) summary of the 22 ranked preclinical preproposals, and (3) all 49 preclinical preproposals. Preproposals listed in the table are identified by an in-house candidate technology (CT) number and key words reflecting the experimental treatment. For those preproposals that were ranked, the expert panel also listed in the table the general type of technology, stage of development, and estimated commercial viability of the product/agent.

Among ten clinical preproposals considered, the expert panel identified the top two. One is an agent that already has FDA approval for use in surgery and the other is an agent progressing to Phase II clinical trials. One of the top two clinical preproposals had an average score of 3.29 for military relevance, a value considered by the expert panel to reflect borderline military relevance.

Among the 49 preclinical preproposals considered, 22 are ranked. These 22 preclinical preproposals are subgrouped into tiers: five in the top tier, nine in the middle tier, and eight in the minor tier. All preproposals in the top tier of total scores also rank in the top eight best for both military relevance and scientific merit. Leading preclinical preproposals include augmented blood volume expanders and adjuncts to resuscitation fluid. LSRO informs the sponsor that the score for CT 023 in the middle tier is based on two of the four models proposed. The expert panel considered only the two hemorrhage models (experimental model numbers 2 and 4) relevant.

The top two preclinical candidates were estimated to be, at best, within four years of clinical trials and the remaining three candidates in the top tier were estimated to be five or more years from clinical trials. The only preclinical preproposal to be scored that was, at best, within two years of clinical trials, was an augmented blood volume expander ranked as the top preproposal in the middle tier.

As is presented in Figure-line graph, all preclinical preproposals scoring in the top tier had better scientific merit than the two leading clinical preproposals. Furthermore, all preclinical preproposals scoring in the top and middle tiers had better military relevance than the two leading clinical preproposals. The lowest ranked preclinical preproposal had average scores of 3.50 and 3.57 for military relevance and scientific merit, respectively. These values are considered by the expert panel to reflect borderline questionable military relevance and scientific merit.

As will be discussed in the full report, many preproposals lacked relevant content and sufficient detail for definitive evaluations. Hence, the scoring of full proposals may differ from that of preproposals, even though similar review criteria may be applied. For similar reasons, differences up to one point in rank order of preproposals may not prove relevant for funding decisions.

In its report, LSRO and the expert panel will be making several recommendations for full proposals to assist you, the offeror, and future peer-review panels. LSRO anticipates that the expert panel will encourage the sponsor to request at least twice as many full proposals as the sponsor intends to fund. Specifically, at a minimum, the sponsor might consider requesting full proposals for the top two clinical candidates and for the 14 preclinical preproposals that scored in the top and middle tiers. In general, the expert panel gave investigators the benefit of the doubt when information was missing from the preproposal. Therefore, the expert panel expects that some studies whose preproposals were scored highly may fall in ranking when the full proposals are reviewed. Other highly ranked studies may not be selected by the military for funding for other reasons, such as cost or projected time delays before the study can commence. The expert panel estimates that a review and ranking of the specified 16 full proposals could be completed by a peer-review panel in a one-day six-hour meeting if the sponsor follows the expert panel's recommendations for the format and content of full proposals.

LSRO anticipates that the expert panel will advise the sponsor to limit the funding cycles of preclinical trials to two years and also limit clinical trials, perhaps to three years. Note that one of the ranking preproposals for clinical trials suggested they may request funding for more than three years and that several ranking preclinical trials had suggested requesting funding for up to three years.

The expert panel informs the sponsor that product development of the experimental therapy in preproposal CT 037 is apparently being partially funded by NIH. The expert panel advises that the sponsor may consider tracking the progress of this anti-inflammatory therapy, which scored in the minor tier.

As a supplement to this letter, we have enclosed a CD containing brief summaries of the expert panel's findings of the strengths and limitations of each preproposal. The expert panel intentionally limited the initial reviewer's comments to brief summaries, to which LSRO added some additional comments from the full expert panel. Also, we are including a table containing the official Army identification numbers. Copies of the 5-page preproposals (as submitted) will be sent to you should you request them.

Regards,

Catherine J. Klein, PhD
Senior Staff Scientist and Project Leader
Life Sciences Research Office
(301) 634-7032
kleinc@LSRO.org

Enclosure: Table of provisional DRAFT results: panel scores of preproposals
Figure-line graph
Table of candidate submissions (official identification information)
CD of summary critiques of individual preproposals

APPENDIX D. MEETINGS OF THE EXPERT PANEL

D.1 January 2005 Meeting Minutes

Minutes of the AFRRF Expert Panel Meeting: January 10-11, 2005

(http://www.lsro.org/resusc/meetings/m_2005_01_10/frames_home.html)

Attendees

Panel Members

Bradley A. Boucher, Pharm.D., F.C.C.P., F.C.C.M., B.C.P.S.

Kenneth E. Burhop, Ph.D.

James W. Holcroft, M.D. (Chair)

Jureta W. Horton, Ph.D.

John A. Kellum, Jr., M.D., F.A.C.P., F.A.C.C.P., F.C.C.M.

Donald S. Prough, M.D.

Ori D. Rotstein, M.D., F.R.C.S.C., F.A.C.S.

William J. Sibbald M.D., M.P.H., F.R.C.P.C., F.C.C.H.S.E. (teleconference)

Presenters

COL Robert H. Vandre, D.D.S.

COL James L. Atkins, M.D., Ph.D., F.A.C.P.

COL David Graham Burris, M.D., F.A.C.S., D.M.C.C.

Charles E. Wade, Ph.D.

William H. Howell, M.S.

Other Participants

CAPT Stephen T. Ahlers

Hasan B. Alam, M.D., F.A.C.S.

Elizabeth Barrows, M.S.

CAPT Jurandir J. DalleLucca

Dr. Michael B. Given, Ph.D.

Richard McCarron, Ph.D.

COL Rodney A. Michael, M.D.

LSRO Staff

Catherine J. Klein, Ph.D., R.D., C.N.S.D.

Michael Falk, Ph.D.

Karin French, B.S.

Minutes

The Expert Panel for Advanced First-Responder Resuscitation Fluid (AFRRF) met for the first time on January 10-11, 2005 at 9650 Rockville Pike, Bethesda, MD. The Expert Panel members present were Bradley A. Boucher, Kenneth E. Burhop, James W. Holcroft, Jureta W. Horton, John A. Kellum, Jr., Donald S. Prough, and Ori D. Rotstein. One other panel member, William J. Sibbald, was present by teleconference. The LSRO staff present included Catherine J. Klein, Michael Falk, and Karin French.

During the morning session, the sponsor's representatives informed the Expert Panel of military considerations relevant to selection of resuscitation fluid strategies for use by advanced first-responders and delivered the charge to the Expert Panel. Catherine Klein, project leader, handled administrative matters and Michael Falk, Executive Director of LSRO, explained LSRO working methods. The primary discussion topics for the

remainder of the meeting were identifying goals and future needs, forming a work plan, assigning tasks, and undertaking project work. The meeting closely followed its agenda, published elsewhere on this net site. The panel elected James W. Holcroft, M.D. as their Chairman (note: because of scheduling issues, Dr. Sibbald was not present at the time of election).

The following presentations were made by representatives of the sponsor during the morning session:

Sponsor Introductions and Goals by COL Robert H. Vandre

Overview of Resuscitation Fluid Research Program by COL James L. Atkins

Standard of Care for Resuscitation Fluid in Combat by COL David G. Burris

Milestones and Metrics in Resuscitation Fluid R&D by Charles E. Wade, Ph.D.

The Need for Prioritizing Criteria by William H. Howell, M.S.

Sponsor Tasks Panel by COL James L. Atkins

The following presentation was made by LSRO staff:

Considerations for Setting Review Criteria by Catherine J. Klein, Ph.D.

SIGNED:

James W. Holcroft, M.D.

Chair

D.2 March 2005 Meeting Minutes

Minutes of the AFRRF Expert Panel Meeting, Dallas, TX, March 7-8, 2005

(http://www.lsro.org/resusc/meetings/m_2005_03_07/frames_home.html)

Attendees

Panel Members

Bradley A. Boucher, Pharm.D., F.C.C.P., F.C.C.M., B.C.P.S.

Kenneth E. Burhop, Ph.D.

James W. Holcroft, M.D. (Chair)

Jureta W. Horton, Ph.D

John A. Kellum, Jr., M.D., F.A.C.P. F.A.C.C.P., F.C.C.M.

Donald S. Prough, M.D.

Ori D. Rotstein, M.D., F.R.C.S.C., F.A.C.S.

LSRO Staff

Catherine J. Klein, Ph.D., R.D., C.N.S.D.

Michael Falk, Ph.D.

Minutes

The Expert Panel for Advanced First-Responder Resuscitation Fluid (AFRRF) met for the second time on March 7-8, 2005 in Dallas, TX. The Expert Panel members present were Bradley A. Boucher, Kenneth E. Burhop, James W. Holcroft (Chair), Jureta W. Horton, John A. Kellum, Jr., Donald S. Prough, and Ori D. Rotstein. One other panel member, William J. Sibbald, was unavailable to meet. The LSRO staff members present were Catherine J. Klein and Michael Falk.

The panel reviewed and ranked individual pre-proposals. The meeting closely followed its agenda, published elsewhere on this net site. Catherine J. Klein handled administrative matters.

The following presentations were made by LSRO staff (Catherine J. Klein, Ph.D.):

Submissions and exclusions

Initial review criteria and further considerations

SIGNED:

James W. Holcroft, M.D.

Chair

D.3 June 2005 Meeting Minutes

Minutes of the AFRRF Expert Panel Meeting: June 23, 2005

Attendees via teleconference

Panel Members

James W. Holcroft, M.D. (Chair)

Jureta W. Horton, Ph.D

John A. Kellum, Jr., M.D., F.A.C.P., F.A.C.C.P., F.C.C.M.

Ori D. Rotstein, M.D., F.R.C.S.C., F.A.C.S.

Sponsor Representatives

COL James L. Atkins, M.D., Ph.D., F.A.C.P.

Dr. Michael B. Given, Ph.D.

Elizabeth Barrows, M.S.

LSRO Staff

Catherine J. Klein, Ph.D., R.D., C.N.S.D.

Michael Falk, Ph.D.

Karin French, B.S.

Minutes

The Expert Panel for Advanced First-Responder Resuscitation Fluid (AFRRF) met for the third time on June 23, 2005 via teleconference from 2:00 to 3:15 pm ET. The expert panel members participating were James W. Holcroft, Jureta W. Horton, John A. Kellum, Jr., and Ori D. Rotstein. The LSRO staff present included Catherine J. Klein, Michael Falk, and Karin French.

During the first 45-minute session, the sponsor's representatives informed the expert panel of their plans for inviting full proposals on resuscitation fluid and adjunct therapies and obtained feedback from the expert panel. The primary discussion topics for the remainder of the meeting were finalizing recommendations and the report, and forming a work plan for review of full proposals if the LSRO contract is extended. Catherine Klein, project leader, handled administrative matters.

SIGNED:

James W. Holcroft, M.D.

Chair

APPENDIX E. PATIENT FLOW IN A THEATER OF OPERATIONS

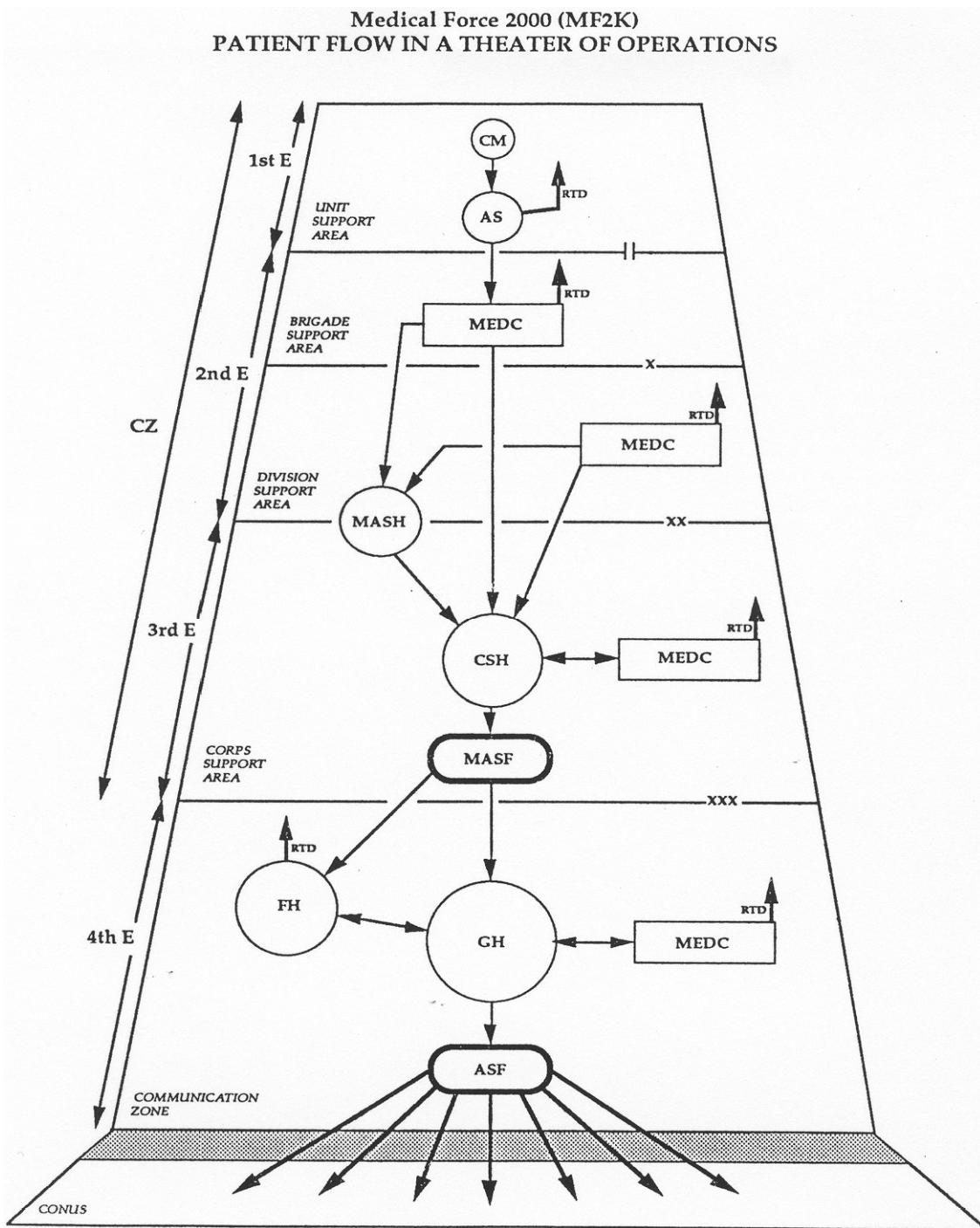


Figure E.1 Patient flow in a hypothetical theater of operations. This diagram represents the traditional scheme of medical support. AS: Aid station; ASF: Aeromedical Staging Facility, USAF; CM : Combat medic; CSH: Combat Support Hospital; CZ: Combat zone; E: Echelon; FH: Field hospital; GH: General hospital; MASF: Mobile Aeromedical Staging Facility, USAF; MASH: Mobile Army Surgical Hospital; MEDC: Medical Company; RTD: Return to duty; USAF: United States Air Force. Credit: Zajtchuk, *et al.*, 1991.

APPENDIX F. PROPOSAL INSTRUCTIONS AND FORMS

Note that the copies of forms in this report were modified in size and margins to fit the LSRO report formatting requirements and are not valid for actual submission purposes. Valid originals will be provided to the sponsor as a supplement to this report.

F.1 Proposal Instructions

INSTRUCTIONS FOR SUBMISSION OF PROPOSALS TO USAMRMC FOR ADVANCED FIRST-RESPONDER RESUSCITATION FLUIDS AND ADJUNCT THERAPIES

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- III.7.2 Preliminary Data

III.7.3 Research Design and Methods

III.7.3.1 Protection of Human Subjects

III.7.3.2 Use of Vertebrate Animals

- III.8 Research Bibliography
- III.9 Acronym/Symbol Definition
- III.10 Budget Instructions (Form H and Form I)
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- III.12 Existing/Pending Support and Past Related Efforts
- III.13 Consortium/Contractual Arrangements for Proposed Research
- III.14 Letters Confirming Collaboration
- III.15 Available Facilities and Major Equipment (Form K)
- III.16 Institution Safety Program Plan
- III.17 Certificate of Environmental Compliance
- III.18 Human Use Required Information and Approval
- III.19 Animal Use Required Information and Approval
- III.20 Appendix

I. FORMS AND SUBMISSION INFORMATION

I.1 Access to Instructions and Forms

All pages of the completed preproposal/proposal should comply with formatting requirements.

Preproposals/proposals submitted for Advanced-First Responder Resuscitation Fluid (AFRRF) awards have specific requirements that are in addition to the U.S. Army Medical Research and Materiel Command (USAMRMC) general requirements.

The forms in this proposal packet are tailored to the AFRRF award. Supplemental instructions and forms for USAMRMC general awards (*i.e.*, Appendices 1-11) are available at: http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm, which can be used in place of the AFRRF formats, as long as the requested AFRRF information and AFRRF defined page limitations are followed. These forms are interactive and may be completed electronically for inclusion on a CD/DVD for submission.

- If you have questions concerning the preparation of preproposals or proposals, please contact: Cheryl Miles, 301-619-7148, cheryl.miles@det.amedd.army.mil

I.2 Mailing Instructions

- Follow mailing directions as indicated for other USAMRMC awards and submit the preproposal or full proposal with appendices on one CD/DVD in PDF or Microsoft® Word format. Label the disk with the name of the principal investigator and organization and the email address and phone number of a point-of-contact individual.

Mail, courier, or hand-deliver submissions to:

USAMRAA
 ATTN: [add announcement number here, e.g., W81XWY-BAA 04-1-AFRRF]
 820 Chandler Street
 Fort Detrick, MD 21702-5014

II. INSTRUCTIONS FOR PREPARING THE AFRRF PROPOSAL PACKET

- These instructions pertain to applications to USAMRMC for research project awards for AFRRF therapies. These instructions are meant to comply with USAMRMC proposal requirements
- Forms specific to the AFRRF proposal are available in Microsoft® Word and PDF formats.
- All requested information must be submitted in English in the format required.
- Preproposals are to follow the same formatting and content requirements as full proposals, except where noted. For example, preproposals have different page limitations. (See Table 1.)

II.1 Proprietary and Confidential Information

- Offerors are discouraged from submitting information considered proprietary or confidential unless it is deemed essential for proper evaluation of the proposal. However, when the proposal contains information that constitutes trade secrets, or information that is confidential or privileged, mark the pages **CONFIDENTIAL**.

II.2 Format Specifications

The proposal must contain only material that reproduces well when photocopied in black and white. Do not use photo reduction.

II.2.1 Format Pages

- Format pages (forms) are available for eleven (11) major sections of the proposal packet as indicated in Table 1. Other required forms are available from USAMRMC (*i.e.*, Appendices 1-11, http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm). These forms are intended to assist in the development of specific sections of the proposal. Alternatively, you may create a page similar to any format provided as long as all the requisite information is included and format requirements are met.

II.2.2 Font

- Adherence to font and margin requirements is mandatory.
- Suggested typeface: Arial, Helvetica, Palatino Linotype or Georgia.
- Use a font size of 12 points. You may use a smaller font size for figures, figure legends, graphs, diagrams, charts, tables, and footnotes but it must be in black ink, and readily legible.
- Type density of line must be no more than 15 (total) characters per horizontal inch, including the spaces between words and punctuation.
- The proposal must be single-spaced having a line density per page of no more than five (5) lines per vertical inch.
- Use black ink that can be clearly copied.
- Print must be clear and legible.

II.2.3 Page Size, Margins, Pagination, and Running Header

- Use standard 8 1/2" x 11" page size.
- Use at least one-half inch margins for top, bottom, and right and one inch left margins for all pages, including continuation pages and the Appendix. Print area should be no more than 7.0 x 10.0 inches (approximately 18 cm x 25.5 cm).
- The proposal must be single-sided (except the Appendix can be double-sided).
- All pages must be numbered (except the Appendix can be unnumbered). Center numbers at the bottom of the page; make sure numbers do not enter into the one-half inch bottom margin.
- Follow Table of Contents format (Form C) to order pages in the proposal, which is the same as the organization of major sections in Table 1. Beginning with the Proposal Cover Page, consecutively number pages throughout the proposal including continuation pages. Do not use suffixes (*e.g.*, do not use 5a, 5b). List the assigned page numbers for all major headings of the proposal packet in the Table of Contents (Form C).
- Beginning with page two (2) of the proposal, specify the name of the Principal Investigator or Program Director at the top of every page as a running header, including continuation pages and Appendix pages, making sure that names do not enter into the one-half inch top margin.

II.2.4 Abbreviations, Acronyms, and Symbols

- Unless the abbreviation, acronym or symbol is universally known, spell out the term and note its abbreviation in parentheses the first time the term is used. All abbreviations used in the Abstract, Product/Agent, Military Relevance, and Research Plan sections of the proposal must be defined the first time they are used in each of these sections.
- List abbreviations, acronyms, and symbols on one page following the Research Bibliography.

II.2.5 Page Limitations

- All proposals must be self-contained within specified page limitations given in Table 1. Hence, content displayed at Internet website addresses (*i.e.*, URLs) may not be used to provide information necessary to the review. Note that reference to such a website could compromise the offeror's anonymity.
- Proposals that exceed the page limitations will be returned without review.

Table 1. Forms, Page Limitations, and Related Specifications

<u>Section</u>	<u>Form</u>	<u>Page Limit, Proposal (Preproposal)</u>	<u>Related Specifications</u>
Proposal Cover Page	A	1	Do not exceed 120 characters in the title of research project, including the spaces between words and punctuation
Abstract, Performance Sites, Key Personnel, Other Significant Contributors	B	None	<u>Abstract must not exceed space provided on Form B</u>
Table of Contents	C	None	
Statement of Work	D	1	
Product/Agent	E	2 (1)	
Military Relevance of Product/Agent	F	1	
Research Plan	G	Total = 8 (4)	Page limits are for all text, figures, charts, tables, and diagrams included in the Research Plan.
Specific Aims, Background, and Significance sub-section limit:		2 (1)	
Preliminary Data sub-section limit:		2 (1)	
Research Design and Methods sub-section limit:		4 (2)	
Research Bibliography	None	None	<u>Each continuation page must bear the heading: Research Bibliography</u>
Acronym, Definition	Symbol	None	None
Detailed Cost Estimate for Initial 12 Month Budget Period	H	None	
Summary Budget for Entire Proposed Period of Support	I	None	
Budgets Pertaining to Consortium/Subawards	H/I	None	
Biographical Sketches of Key Personnel and Other Significant Contributors	J	3 (2) per individual	
Existing/Pending Support and Past Related Efforts	None	None	
Consortium/Contractual Arrangements for Proposed Research	None	None	
Letters Confirming Collaboration	None	None	<u>(Full proposals only)</u>
Available Facilities and Major Equipment	K	None	
Institution Safety Program Plan	Available	None	<u>(Full proposals only)</u> See Appendix 11 of the USAMRMC general proposal instructions and forms.*

Table 1. (continued)

<u>Section</u>	<u>Form</u>	<u>Page Limit, Proposal (Preproposal)</u>	<u>Related Specifications</u>
Certificate of Environmental Compliance	Available	None	(Full proposals only) Submit one certificate for each site conducting research under the proposal, including subcontractors. See Appendix 8 of USAMRMC general proposal instructions and forms.*
Human Use Required Information and Approval	Available	None	(Full proposals only) See Appendix 9 of the USAMRMC general proposal instructions and forms. Must be submitted within 60 days of award if proposal is approved for funding.*
Animal Use Required Information and Approval	Available	None	(Full proposals only) See Appendix 10 of the USAMRMC general proposal instructions and forms. Must be submitted within 60 days of award if proposal is approved for funding.*
Appendix	None	None	(Full proposals only) Appendix material might not be reviewed. Hence, do not include in the Appendix experimental data or other information critical to the review. <u>Do not use the Appendix to circumvent the page requirements of the body of the proposal.</u> Indicate conclusion of Appendix material with a line stating "END OF APPENDIX MATERIAL"

*http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm

III. INSTRUCTIONS FOR SPECIFIC ITEMS

Follow instructions on proposal forms. Additional instructions are provided below to assist in form completion.

III.1 Proposal Cover Page (Form A)

• The entire Proposal Cover Page (page 1 Form A) must be printed on a single page. The Proposal Cover Page must not have any shading or colors.

- Indicate whether this is a preproposal or full proposal.
- Choose a descriptive title that is specifically appropriate.
- If this proposal is in response to a specific request or Broad Agency Announcement (BAA), insert the appropriate announcement number and title of that announcement.
- If this proposal follows the previous submission of a preproposal of the same project, provide the USAMRMC assigned log number and title of the previous preproposal.

III.1.1 Cover Page Item 3: Principal Investigator/Program Director

- The name of the Principal Investigator/ Program Director should be the one person responsible to the applicant organization for the scientific and technical direction of the project.
- Indicate up to three academic and professional degrees or other credentials, such as licenses (e.g., R.N.).
- Provide the academic or professional title of the Principal Investigator/Program Director. If there is more than one position title, indicate the one most relevant to the proposed project (e.g., Chief of Surgical Service).
- Indicate the school, college, or other major subdivision, such as medical, engineering, graduate, or nursing. If there is no such subdivision, enter "None."

III.1.2 Cover Page Item 4: Human Subjects Research

Research that involves obtaining private information or identifiable human biological specimens (such as blood and tissue samples) is considered human subjects research (45 CFR Part 46).

- Answer "Yes" if research activities involving human subjects are planned at any time during the proposed project period, even if the research is exempt from regulations for the protection of human subjects. Note: use of cadaver specimens are not human subjects research.
- If the study might involve human subjects during the proposed project period, but does not have definite plans at the time of application, the Principal Investigator will need to provide the Research Plan before the research can occur.
- Enter the institution's current Multiple Project Assurance (MPA) or Federal Wide Assurance (FWA) number with the U.S. Department of Health and Human Services Office for Human Research Protections in item 4a. See section III.18 on Human Use Required Information and Approval. See supplemental instructions in Appendix 9 of the general USAMRMC proposal instructions particularly part 12, Assurances, and part 3-c, Multi-site Protocol Review, at http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm

III.1.3 Cover Page Item 5: Use of Vertebrate Animals

- Enter the Institutional Animal Care and Use Committee (IACUC) approval date in item 5b if such approval has been obtained. IACUC protocol review and approval may follow proposal submission for peer review but must be provided prior to Department of Defense approval of the proposed animal research. See section III.19 on Animal Use Required Information and Approval. See supplemental instructions in Appendix 10 of the general USAMRMC proposal instructions particularly part 13 on IACUC approval at http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm

III.1.4 Cover Page Item 6, Item 7, and Item 8: Dates and Budget of Proposed Period of Support

- For duration (in years), allow time to complete research efforts and complete final report. Request no more than 2 years of support for non-clinical studies and no more than 3 years of support for human clinical studies. Note: Some mechanisms specify fewer years.
- Proposal valid until date: allow a minimum of six months from the date of submission.
- Dollar amounts must be in U.S. dollars.
- Initial budget period refers to the first 12 month funding period. These direct and total costs are derived from Form H.
- The direct and total costs of the proposed period of support are derived from Form I.

III.1.5 Cover Page Item 9 to Item 12: Applicant Organization and Authorized Representative

- Awards are made to organizations, not individuals. Any organization receiving an award under the BAA must be registered in the Central Contractor Registration database, which requires a Data Universal Numbering System (DUNS) number. Registration may be accomplished online via the internet at <http://www.ccr.gov/>
- For entity identification of the organization, enter the DUNS number. The DUNS is a nine-digit Universal Identifier number assigned by Dun and Bradstreet Information Services. If the organization does not have a DUNS number, an authorized organizational official should complete the electronic US D&B D-U-N-S Number Request Form or call 1-866-705-5711 (toll-free) to obtain an organizational number immediately at no charge. Principal investigators do not need to register for an individual DUNS number.
- Name the authorized representative of the one organization that will be legally and financially responsible for the conduct of activities supported by the award (Item 10).
- Enter the name and contact information for an alternate Principal Investigator (Item 11) and alternate organizational representative (Item 12).

III.1.6 Cover Page Item 13 and Item 14: Official Signatures

- Electronic signatures are acceptable or the signed forms can be scanned and included in the proposal.
- "Per" signatures (signing as the designated official or without the formal delegation) are not acceptable. The date of signature must be included.
- "For" signatures are acceptable for Item 14 only (i.e., if the official designated to sign for the applicant organization is not available to sign) only another institutional official with formal delegated authority to act in his/her behalf may sign as "acting for" such official. ***In signing the Proposal Cover Page, the duly authorized representative of the applicant organization certifies that the applicant organization will comply with all applicable policies, assurances and/or certifications referenced in the proposal.*** The applicant organization is responsible for verifying its eligibility and the accuracy, validity, and conformity with the most current institutional guidelines of all the administrative, fiscal, and scientific information in the proposal, including the Facilities and Administrative rate. Deliberate withholding, falsification, or misrepresentation of information could result in administrative actions, such as withdrawal of a proposal, suspension and/or termination of an award, debarment of individuals, as well as possible

criminal penalties. The signer further certifies that the applicant organization will be accountable both for the appropriate use of any funds awarded and for the performance of the grant-supported project or activities resulting from this proposal. The grantee institution may be liable for the reimbursement of funds associated with any inappropriate or fraudulent conduct of the project activity.

III.2 Abstract, Performance Sites, Key Personnel, Other Significant Contributors (Form B)

Do NOT insert additional pages between Proposal Cover Page 1 (Form A) and Page 2 (Form B). Information for the non-abstract sections of Form B can be continued on consecutively numbered pages.

III.2.1 Abstract: Project Summary and Relevance

- Do not exceed the defined space provided for the abstract on Form B. This space is 6.25 inches horizontal by 6.5 inches vertical.
- The abstract serves as a succinct and accurate description of the proposed work when separated from the proposal. As instructed on Form B, be sure to identify the product/agent to be tested and the relevance of the project to the treatment of hemorrhagic shock and to combat casualty care. State what is unique and innovative about your approach. Avoid describing past accomplishments and the use of the first person.
- Spell out all Greek or other non-English letters.
- Do not include figures or tables in the abstract.
- Do not include proprietary, confidential information or trade secrets in the abstract or information subject to restrictions on distribution for evaluation purposes.

At the time these instructions were prepared, a direct link to an example abstract was not available, but an example of a general USAMRMC technical abstract could be viewed from the URL <http://www.usamraa.army.mil/pages/index.cfm> by selecting "BAA" then selecting "USAMRMC" then selecting the preferred format for the Sample Technical Abstract.

III.2.2 Performance Site(s) of Proposed Research

- If there is more than one performance site where the work described in the Research Plan (Form G) will be conducted, list all the sites, including the Department of Veterans Affairs (V.A.) facilities and foreign sites, and provide an explanation in the Available Facilities and Major Equipment (Form K) section of the proposal. One of the sites indicated must be the applicant organization. Additional information about the performance sites is also detailed in section III.15 on Available Facilities and Major Equipment.

III.2.3 Key Personnel

- In addition to the Principal Investigator, Key Personnel are defined as individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries are requested. Typically, these individuals have doctoral or other professional degrees, although individuals at the masters or baccalaureate level should be included if their involvement meets the definition of Key Personnel. **Consultants should also be included if they meet the same definition.**
- "Zero percent" effort or "as needed" are not acceptable levels of involvement for those designated as Key Personnel.
- Key Personnel are expected to work collaboratively and collectively maintain sharp focus toward achieving project objectives.
- Letters of support from Key Personnel are to be included as described in Letters Confirming Collaboration (full proposals only).

III.2.4 Other Significant Contributors

- This category identifies individuals who have committed to contribute to the scientific development or execution of the project, but are not committing any specified measurable effort to the project. These individuals are typically presented at "zero percent" effort or "as needed." Do not list individuals with measurable effort as Other Significant Contributors. Examples of Other Significant Contributors include consultants and mentors on Career awards.
- Should the level of involvement change for an individual listed in this category, they should be redesignated as Key Personnel before any compensation is charged to the project.

III.3 Table of Contents (Form C)

- The research proposal should be organized by placing major sections in the order listed in Table 1 and Form C. List the page number for each major heading in the Table of Contents. (For pagination see section II.2.3.)

III.4 Statement of Work (Form D)

- Do not exceed one page.
- The instructions on Form D for the Statement of Work (SOW) are consistent with the USAMRMC proposal preparation instructions. The SOW outlines performance expectations for the project within the timeframe of the budget period.
- At the time these instructions were prepared, a direct link to an example SOW was not available, but one could be viewed from the URL <http://www.usamraa.army.mil/pages/index.cfm> by selecting “BAA” then selecting “USAMRMC” then selecting the preferred format for the Sample Statement of Work. This sample is presented in Figure 1.

SAMPLE

Statement of Work

Development of Peptide Inhibitors of the “Cancer” Receptor (CR)

Task 1. To identify the minimal region of the CR polypeptide able to inhibit intact CR when co-expressed in cultured cells (Months 1-18):

- Develop a series of plasmids for expressing the CR open reading frame (Months 1-7).
- Perform assays to ascertain which fragments of CR block DNA-binding (Months 7-18).
- Confirm that fragments of the CR open reading frame that block DNA-binding activity also inhibit CR function *in vivo* (Months 18-24).

Task 2. To identify short peptides modeled after the receptor that act as inhibitors of DNA-binding and subunit association (Months 18-26):

- Obtain synthetic CR peptides (Months 18-21).
- Test the effect of synthetic peptides on the DNA-binding activity of CR (Months 20-24).
- Characterize the inhibitory potency of active peptides and attempt to optimize the effect by testing additional overlapping peptides (Months 21-36).
- Perform feasibility experiments to assess the ability of selected peptides to inhibit CR function in cultured cells (Months 20-36).

Figure 1. An example Statement of Work presented by the U.S. Army Medical Research and Materiel Command (<http://www.usamraa.army.mil/pages/index.cfm>).

III.5 Product/Agent (Form E)

- Do not exceed 2 pages for full proposals or 1 page for preproposals.
- The references cited on Form E *should be limited to relevant and current literature*. These references should be listed in the Research Bibliography.

III.5.1 Product/Agent: Identity and Characterization

- Provide salient characteristics of the product/agent particularly information useful for assessing its military relevance. Briefly describe preparation and route of administration, safety data, pharmacodynamics and mechanism of action. Of particular interest is whether there is a biohazard from expired, crushed/damaged, leftover product. The offeror should mention if the product requires special storage, transport, or use conditions.

III.5.2 Product/Agent: Timeline of Product Development

- Outline a timeline of product development from current stage to the next logical clinical phase (e.g., Phase I trial). Note any ongoing or planned clinical trials. The timeline should be clearly articulated. Do not confuse this timeline of product development with the tentative timetable for the proposed project in the Research Plan.
- Identify the product/agent’s current status in the U.S. Food and Drug Administration’s approval process with respect to the intended purpose as proposed in this application as well as for other intended purposes, including approved route(s) of administration. If product/agent is not approved for use in the United States but is in the European market, note this.
- Succinctly state how the proposed project will further the product/agent’s development.

III.5.3 Product/Agent: Manufacturer

- If the product manufacturer is also a partner in the project contributing to the scientific development or execution of the project in a substantive, measurable way their representative should be listed with Key Personnel or Other Significant Contributors on Form B.
- If the product manufacturer is donating product for use in the project, this should be indicated in the budget (Form H) under supplies or patient care costs.

III.5.4 Product/Agent: Intellectual Property Protection

- List the relevant contractual issues of the focal products/agents, such as patents.

III.5.5 Product/Agent: Outline Process for Commercial Development

- Provide information that supports the commercial appeal and viability of the proposed product/agent in the non-military environment. If there is a commercial development plan, provide a brief outline of this process.

III.6 Military Relevance of Product/Agent (Form F)

- Do not exceed 1 page.
- Using product/agent information from Form E, compare the proposed product/agent to the military product "requirements" or performance goals specified in the specific Broad Agency Announcement or Request for Information to which you are responding. For example, discuss storage and transport requirements, shelf-life/stability under extreme environmental conditions, impact of its weight and volume per unit dose to the soldier who transports it, and its safety and ease of use by first-responders on the battlefield (i.e., its functionality in the combat environment).

III.7 Research Plan (Form G)

Do not exceed eight (8) pages for full proposals or four (4) pages for preproposals. All tables, graphs, figures, diagrams, and charts must be included within the page limit. Proposals that exceed the page limits will be returned without review.

- The Research Plan should include sufficient information needed for evaluation of the project, independent of any other document (e.g., previous proposal). The format for preparing this section is provided on Form G. Be specific, informative and avoid redundancies.
- Full-sized glossy photographs of material such as electron micrographs or gels may be included in the Appendix; however, a photocopy of each must also be included within the page limitations of the Research Plan.
- Offerors are discouraged from submitting information considered proprietary unless it is deemed essential for proper evaluation of the proposal. However, when the proposal contains information that constitutes trade secrets, or information that is confidential or privileged, mark the pages "**CONFIDENTIAL**."
- The references cited in the Research Plan should be limited to relevant and current literature. These references should be listed in the Research Bibliography.

III.7.1 Research Plan: Specific Aims, Background and Significance

- Do not exceed 2 pages for full proposals or 1 page for preproposals.
- State the goal of the specific research proposed and hypothesis to be tested.
- Briefly sketch the background leading to the present proposal, critically evaluate existing knowledge, and specifically identify the gaps that the project is intended to fill.
- What is the proposed mechanism of action of the experimental product/agent for use in resuscitation therapy?
- If the aims of the proposal are achieved, state how scientific knowledge or clinical practice will be advanced. Describe the relevance of the project to the treatment of hemorrhagic shock under combat conditions.
- How is this approach unique and innovative? Describe the effect of these studies on the concepts, methods, technologies, treatments, or services that drive this field.

III.7.2 Research Plan: Preliminary Data

- Do not exceed 2 pages for full proposals or 1 page for preproposals.
- Provide an account of the Principal Investigator/Program Director's preliminary studies and preliminary data pertinent to this proposal. Demonstrate that the product can be administered under circumstances proposed.

III.7.3 Research Plan: Design and Methods

- Do not exceed 4 pages for full proposals or 2 pages for preproposals.
- Particular attention will be paid to proposed experiments that might indicate functionality in a combat-injury environment.
- Describe the research design, procedures, and analyses to be used to accomplish the specific aims of the project in sufficient detail for evaluation. Include how the data will be collected, analyzed, and interpreted as well as the data-sharing plan as appropriate.
- Specify the type and number of subjects to be studied and for clinical studies, specify the power analysis. Define the end points and the statistical protocols and analysis.
- Describe any novel concepts, approaches, tools, or technologies for the proposed studies and its advantage over existing methodologies.
- Discuss the potential difficulties and limitations of the proposed procedures and alternative approaches to achieve the aims. Factors that impact the evaluation of the proposal quality include whether the limitations and uncertainties of the experiment are addressed and whether there is bias, critical omissions, oversights, and/or inconsistencies.

- Point out any procedures, situations, or materials that may be hazardous to personnel and the precautions to be exercised.
- As part of this section, provide a tentative timetable for the proposed project. Do not confuse this project timetable with the timeline of product development in the Product/Agent section of the proposal.

III.7.3.1 Research Plan: Protection of Human Subjects

- For all research involving human subjects, a part of the peer review process will include careful consideration of the protections from research risks, as well as the appropriate inclusion of women and minorities, based on the information in the proposal.
- If you plan to enroll subjects without individual informed consent (*i.e.*, enrollment during the pre-hospital phase of emergency care) discuss any obstacles that might impede the experimental treatment from realistically securing “community consent” (*i.e.*, approval by representatives of the community charged with evaluating product safety data).
- If you are planning a clinical trial, provide a general description of your Data and Safety Monitoring Plan that will be used to provide oversight and monitoring of the safety of participants and the validity and integrity of the data.
- Should the proposal be accepted for funding, human use information will be required within 60 days of the award. See section III.18 on Human Use Required Information and Approval.

III.7.3.2 Research Plan: Use of Vertebrate Animals

- If the use of vertebrate animals is planned, discuss how the animal model is relevant to the military condition (*e.g.*, hemorrhagic shock under combat conditions).
- Studies in the late preclinical stage of product development are encouraged to include:
 - Two species of large animals
 - Uncontrolled hemorrhage to reflect battlefield conditions (*i.e.*, short-term) until evacuation (*e.g.*, 6 to 12 hours) long-term, without clamp, without anesthesia as a variable
 - Assess end organ damage
 - Measure increased survival as an end point
- See section III.19 on Animal Use Required Information and Approval for further instructions. Required materials must be submitted within 60 days of award if proposal is approved for funding.

III.8 Research Bibliography

- Conform to formatting requirements of the proposal packet (*e.g.*, page margins, page numbering). **Each continuation page in this section must bear the heading of Research Bibliography** to easily distinguish it from the peer-reviewed publication sections of the biographical sketches of Key Personnel/Significant Contributors.
- The reference citations should be limited to relevant and current literature. Include references cited in sections Product/Agent (Form E), Military Relevance of Product/Agent (Form F) and Research Plan (Form G) of the proposal packet. While there is not a page limitation, it is important to be concise and to select only those literature references pertinent to the proposed research.
- Each reference citation must include the title, names of all authors, book or journal, volume number, page numbers, and year of publication.
- Do not send or attach copies of articles.

III.9 Acronym/Symbol Definition

- Provide a glossary of acronyms and symbols that might not be familiar to reviewers who are not current in the proposal's research area.

III.10 Budget Instructions (Form H and Form I)

- All proposals should submit Form H: Detailed Cost Estimate for Initial 12 Month Budget Period, **and** Form I: Summary Budget for Entire Proposed Period of Support.
- Follow instructions for Detailed Cost Estimate in section F on pages 18 to 22 of the USAMRMC proposal preparation instructions http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm for information to complete the budget and conform to regulations and principles that apply to commercial firms, educational institutions, nonprofit organizations, and state, local, and tribal governments.
- List only the direct costs requested in this proposal. Do not include any items that are treated by the applicant organization as facilities and administrative (*i.e.*, indirect costs (F&A) costs) according to a federal rate negotiation agreement. However, do include F&A of consortium/contractual participants. F&A costs will NOT be paid on construction grants, grants to Federal organizations, grants to individuals, and conference grants.
- Each item listed on Form H must be clearly justified on Form I, including items categorized as Other Expenses. For offerors performing outside of the United States, justify conversion rates used to convert local currency into U.S. dollars.
- Values in the “Total” column of the initial budget period direct costs on Form H are carried over and entered into the respective column on Form I.

- Enter the total annual costs for additional years of support on Form I. Request no more than 2 total years of support for non-clinical studies and no more than 3 total years of support for human clinical studies.

III.10.1 Budget: Additional Instructions for Patient Care Costs

- If inpatient and/or outpatient costs are requested, provide the names of any hospitals and/or clinics and the amounts requested for each on Form I under Justification.
- Indicate, in detail, the basis for estimating costs in this category, including the number of patient days, estimated cost per day, and cost per test or treatment. If both inpatient and outpatient costs are requested, provide information for each separately. If multiple sites are to be used, provide detailed information by site.
- Include information regarding projected patient accrual for the project/budget periods and relate this information to the budget request for patient care costs. If patient accrual is anticipated to be lower at the start or during the course of the project, plan the budget(s) accordingly.
- Provide specific information regarding anticipated sources of other support for patient care costs (e.g., third party recovery or pharmaceutical companies).

III.10.2 Budget: Additional Instructions for Consortium/Contractual Costs

- The applicant organization should note the sum of direct costs of all consortium/contractual participants and the sum of F&A costs of all consortium/contractual participants on Form H and on Form I. When there are F&A costs for a consortium organization, provide the F&A cost base and rate in the Justification section of Form I.
- In the proposal, include a separate detailed budget (Form H) for each participating consortium/contractual organization. For each, label that page accordingly with name of the organization at the top of the page. If consortium activity exceeds one year, also include Form I for that organization.

III.11 Biographical Sketch (Form J)

- Include Biographical Sketches of all Key Personnel and Other Significant Contributors, including consultants, following the order as listed on Form B. The Biographical Sketch may not exceed 3 pages per individual for full proposals and 2 pages for preproposals.
- Use the heading Selected Peer-Reviewed Publications by Key Personnel/Significant Contributors for the list of selected peer-reviewed publications and also insert this heading at the top of the continuation page if the section is continued. Such a heading easily distinguishes this list from the Research Bibliography section of the proposal packet.
- Current Research should highlight your recent scientific accomplishments. This information is used by the reviewers to assess each individual's qualifications for a specific role in the proposed project, as well as to evaluate the overall qualifications of the research team.

III.12 Existing/Pending Support and Past Related Efforts

- For the Principal Investigator and Key Personnel, list the title, time commitments, supporting agency and level of funding for all existing and pending research projects. Provide justification for USAMRMC support where the projects overlap or parallel.
- Prepare a synopsis of grants on similar or related effort for the past 3 years, including:
 - Specifics on each grant, including types and dates of performance
 - The name and address of the Procuring Contracting/Grant Officer
 - The negotiated price, and the final cost to the Government, with reasons for any variance

III.13 Consortium/Contractual Arrangements for Proposed Research

- Explain the programmatic, fiscal, and administrative arrangements to be made between the applicant organization and the consortium organization(s). If consortium/ contractual activities represent a significant portion of the overall project, explain why the applicant organization, rather than the ultimate performer of the activities, should be the grantee.

III.14 Letters Confirming Collaboration

- (Full proposals only) Include letters of support from Key Personnel.
- Include letters from all consultants that confirm their roles in the project and their rate/charge for consulting services.
- Include a letter of support from the product manufacturer, if indicated on Form E.
- Follow instructions for Collaboration and Joint Sponsorship in part G, item 5 on page 22 of the USAMRMC proposal preparation instructions http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm**

III.15 Available Facilities and Major Equipment (Form K)

- In describing the scientific environment in which the work will be done, discuss ways in which the proposed studies will benefit from unique features of the scientific environment, or subject populations, or the employment of useful collaborative arrangements.

- If proposals include use of Government facilities, offerors will be expected to conclude arrangements for commercial services with the providing Government facility.
- Additional facility information and assurance statements are required for full proposals. See Institution Safety Program Plan.

III.16 Institution Safety Program Plan

- (Full proposals only) Institution-based safety program plan information and assurance statements are required. Follow instructions for Safety Program Plan in Appendix 11 of the USAMRMC proposal preparation instructions http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm to include the required components.

III.17 Certificate of Environmental Compliance

- (Full proposals only) Information regarding environmental compliance must be provided. Follow instructions for Certificate of Environmental Compliance in Appendix 8 of the USAMRMC proposal preparation instructions http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm to include the required components.

III.18 Human Use Required Information and Approval

USAMRMC does not require Institutional Review Board (IRB) approval and certification of the proposed research prior to peer-review of a proposal. Required materials must be submitted within 60 days of award if proposal is approved for funding.

- (Full proposals only) See Appendix 9 of the USAMRMC proposal preparation instructions http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm to include the required components.
- Any modification of the Research Plan section of the proposal required by the IRB or to address human subjects concerns raised during review must be submitted for approval before award.
- If a research proposal involving human subjects, human anatomical subjects, or privileged or protected health information is recommended for funding, a research protocol must be submitted to the Human Subjects Research Review Board (HSRRB) for review and approval. **HSRRB approval must be obtained prior to initiation of Department of Defense sponsored research.**

III.19 Animal Use Required Information and Approval

USAMRMC does not require IACUC approval of the proposed research before peer review of a proposal. Required materials must be submitted within 60 days of award if proposal is approved for funding.

- (Full proposals only) See Appendix 10 of the USAMRMC proposal preparation instructions http://www.usamraa.army.mil/pages/baa_paa/baaproposal.htm to include the required components.
- The principal investigator/program director must submit any modification of the Research Plan section of the proposal required by the IACUC with the follow-up verification.
- Research that generates preclinical safety data intended to support a research or marketing permit for products regulated by the U.S. Food and Drug Administration will be in conformance with Good Laboratory Practices.

III.20 Appendix

- (Full proposals only) Include **five (5) collated sets** of all Appendix material, in the same package with the proposal, following all copies of the proposal. **Do not intermingle Appendix materials with the proposal.**
- The Appendix will not be duplicated with the proposal and will be sent only to primary reviewers of the proposal. Hence, appendix materials might not be reviewed.
- Identify each item in the Appendix with the name of the principal investigator. Appendix material may be single-sided or double-sided and does not require page numbers. Indicate conclusion of Appendix material with a line stating "END OF APPENDIX MATERIAL" after completion of Appendix and within one-half inch margin requirement.
- The following materials may be included in the Appendix:
 - Surveys, questionnaires, data collection instruments, clinical protocols, and informed consent documents. These may be stapled as sets.
 - Original glossy photographs or color images of gels, micrographs, etc., provided that a photocopy (may be reduced in size) is also included within the page limits of the Research Plan. No photograph or color image may be included in the Appendix that is not also represented within the Research Plan.

Do not use the Appendix to circumvent the page limitations of the body of the proposal. Graphs, diagrams, tables, and charts that do not need to be in a glossy format to show detail must not be included in the Appendix. A proposal that does not observe these limitations will be returned.

END OF AFRRF PROPOSAL INSTRUCTIONS

F.2 Proposal Forms

United States Army Medical Research and Materiel Command RESEARCH PROPOSAL COVER PAGE					
This is a: <input type="checkbox"/> Preproposal <input type="checkbox"/> Full Proposal					
1. TITLE (<i>Do not exceed 120 characters, including spaces and punctuation.</i>)					
Supplement to USAMRMC BAA 04-1: Candidate Technologies for Advanced First-Responder Resuscitation Fluid (AFRRF). Funding Opportunity Number: W81XWY-BAA-AFRRF. If a preproposal was previously submitted, enter USAMRMC Log No: and Previous Preproposal Title:					
3. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR (<i>name of Offeror</i>)					
3a. NAME (<i>Last, first, middle</i>)			3b. DEGREE(S)		
3c. POSITION TITLE			3d. MAILING ADDRESS		
3e. DEPARTMENT, SERVICE, LABORATORY, OR EQUIVALENT					
3f. MAJOR SUBDIVISION			E-Mail (<i>Not website URL</i>):		
3g. TELEPHONE AND FAX (<i>Area code, number and extension</i>) Tel: _____ FAX: _____					
4. HUMAN SUBJECTS RESEARCH: <input type="checkbox"/> No <input type="checkbox"/> Yes		4a. Human subjects assurance number:		5a. USE OF VERTEBRATE ANIMALS <input type="checkbox"/> No <input type="checkbox"/> Yes	
		4b. Clinical Trial: <input type="checkbox"/> No <input type="checkbox"/> Yes	4c. Phase III Clinical Trial: <input type="checkbox"/> No <input type="checkbox"/> Yes	5b. IACUC approval date / /	
6a. PROPOSED PERIOD OF SUPPORT (MM/DD/YY)		7. ESTIMATED COSTS FOR INITIAL 12-MONTH BUDGET PERIOD		8. ESTIMATED TOTAL COSTS FOR PROPOSED PERIOD OF SUPPORT	
Earliest start date / /	Duration in years	7a. Direct Costs (\$)	7b. Total Costs (\$)	8a. Direct Costs (\$)	8b. Total Costs (\$)
6b. Proposal valid until: / /					
10. AUTHORIZED REPRESENTATIVE SIGNING FOR APPLICANT ORGANIZATION Name: Title: Mailing Address:					
9a. APPLICANT ORGANIZATION (PI's organization): Tel: FAX: E-mail:					
11. ALTERNATE PRINCIPAL INVESTIGATOR Name: Tel: E-Mail:			12. ALTERNATE REPRESENTATIVE FOR ORGANIZATION Name: Tel: E-Mail:		
13. PRINCIPAL INVESTIGATOR/PROGRAM DIRECTOR ASSURANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. I agree to accept responsibility for the scientific conduct of the project and to provide the required progress reports if a grant is awarded as a result of this application.			SIGNATURE OF PI/PD NAMED IN ITEM 3a. (<i>"For" and "Per" signatures not acceptable.</i>)		DATE / /
14. APPLICANT ORGANIZATION CERTIFICATION AND ACCEPTANCE: I certify that the statements herein are true, complete and accurate to the best of my knowledge, and accept the obligation to comply with US Army Medical Research Acquisition Activity terms and conditions if a grant is awarded as a result of this application. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.			SIGNATURE OF OFFICIAL NAMED IN ITEM 10. (<i>"Per" signatures not acceptable.</i>)		DATE / /
NOTHING ON THIS PAGE IS PROPRIETARY INFORMATION					

Principal Investigator/Program Director (Last, First, Middle):

PROPOSAL TITLE (*Do not exceed 120 characters*):

Keywords (6-8 words):

ABSTRACT: State the proposal's broad, long-term objectives and specific aims, making reference to the relevance of the project to hemorrhagic shock. Identify the product or agent to be tested. Describe concisely the research hypothesis, design, and main methods for achieving these goals. Describe the primary data to be collected. State what is innovative about your approach.

In addition, in two or three sentences, describe in plain, lay language the relevance of this research to combat casualty care. If the proposal is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information.

DO NOT EXCEED THE SPACE PROVIDED (about 200 words):

6.25" x 6.5" (this image not to scale)

NOTHING ON THIS PAGE IS PROPRIETARY INFORMATION

Principal Investigator/Program Director (Last, First, Middle):

PERFORMANCE SITE(S) OF PROPOSED RESEARCH (organization, city, state):

KEY PERSONNEL. Start with Principal Investigator. List all other key personnel in alphabetical order. *Use continuation pages as needed to provide the required information in the format shown below.*

Name (Last, First Middle)	Organization	Role on Project
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OTHER SIGNIFICANT CONTRIBUTORS

Name (Last, First Middle)	Organization	Role on Project
---------------------------	--------------	-----------------

The name of the principal investigator/program director must be provided at the top of each printed page and each continuation page.

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Preliminary Data	_____
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Research Bibliography	_____
Acronym/Symbol Definition	_____
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Summary Budget for Entire Proposed Period of Support (Form I).....	_____
Budgets Pertaining to Consortium/Subaward Contractual Arrangements	_____
Biographical Sketch (Form J)– Principal Investigator/Program Director	_____
Other Biographical Sketches (Form J)	_____
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Consortium/Contractual Arrangements for Proposed Research.....	_____
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Available Facilities and Major Equipment (Form K)	_____
Institution Safety Program Plan (<i>Full proposals only</i>)	_____
Certificate of Environmental Compliance (<i>Full proposals only</i>)	_____
Human Use Required Information and Approval (<i>Full proposals only</i>).....	_____
Animal Use Required Information and Approval (<i>Full proposals only</i>).....	_____
Appendix (<i>Full proposals only</i> . No page numbering necessary for Appendix)	<input type="checkbox"/> Check if Appendix is Included
Other items (list):	

Other items (list):

Principal Investigator/Program Director (Last, First, Middle):

STATEMENT OF WORK

The Statement of Work (SOW) outlines performance expectations for the project within the timeframe of the budget period. List the major performance goals of the proposed research. In a series of short statements, outline the approach that will be taken to achieve these goals. Include specific tasks, systems, and materials that are reasonable estimates for testing the proposed hypotheses of the study. For each year of the contracted project, define the milestones and goals that the principle investigator/applicant organization is expected to meet. The SOW might be incorporated into the award document and, as such, is subject to release under FOIA. Therefore, do not include proprietary/confidential information. **DO NOT EXCEED ONE PAGE.**

NOTHING ON THIS PAGE IS PROPRIETARY INFORMATION

Principal Investigator/Program Director (Last, First, Middle):

Product/Agent

Do not exceed a total of 2 pages for Form E including the continuation page if needed for full proposals or 1 page for preproposals. The citations for publications referred to on Form E should be listed in the Research Bibliography.

PRODUCT IDENTITY (and formulation):**PRODUCT CHARACTERIZATION**

Physicochemical properties (e.g., potency, long-term stability, temperature for storage/transport, solubility, stability after reconstitution):

Pharmacokinetics (bioavailability/absorption, distribution, half-life, metabolism, clearance/excretion):

ADMINISTRATION (route, preparation, volume per unit dose):**SAFETY DATA** (brief overview):**PHARMACODYNAMICS AND MECHANISM OF ACTION** (for treatment of exsanguinating hemorrhage, e.g., volume expander):**PROVIDE A TIMELINE OF PRODUCT DEVELOPMENT** (from current stage to first/next clinical phase):

Is product/agent currently in U.S. market? No Yes If yes, by what route of administration and for what indication(s)? If no, does product/agent have investigational new drug (IND) status for any indication?

PRODUCT MANUFACTURER:

Letter of support from corporate partner included in this proposal (*Full proposals only*): No Yes

Estimated cost range per dose:

INTELLECTUAL PROPERTY PROTECTION RIGHTS/CONTRACTS (e.g., patents):**OUTLINE PROCESS FOR COMMERCIAL DEVELOPMENT:** Is the product/agent sufficiently attractive to industry that it will be commercially viable outside the military environment? What is the plan for taking the product/agent to market?

Principal Investigator/Program Director (Last, First, Middle):

Military Relevance of Product/Agent

Assess the strengths and limitations of use of the product/agent by Combat Casualty Care compared to military product "requirements." Consider first-responder transport, preparation, and safe administration of product. How will they select the patients to whom it should be administered? Does this approach (1) increase the probability of survival from exsanguinating hemorrhage on the battlefield and/or (2) decrease later medical complications? Do not exceed 1 page for Form F. Citations should be listed in the Research Bibliography section of the proposal.

Principal Investigator/Program Director (Last, First, Middle):

Research Plan

Do not exceed 8 pages for full proposals or 4 pages for preproposals. All tables, graphs, figures, diagrams, and charts must be included within the page limit

The citations for publications referred to in the Research Plan should be listed in the Research Bibliography.

Specific Aims, Background and Significance (*Do not exceed 2 pages for full proposals or 1 page for preproposals*)

Specific Aims and Hypothesis:

Background and Significance: Discuss the proposed mechanism of action of the experimental product/agent for use in resuscitation therapy and the relevance of the project to the treatment of hemorrhagic shock under combat conditions. How is this approach innovative?

Preliminary Data (*Do not exceed 2 pages for full proposals or 1 page for preproposals*) Demonstrate that the product can be administered under the circumstances proposed.

Research Design and Methods (*Do not exceed 4 pages for full proposals or 2 pages for preproposals*). Describe the research design and methods in sufficient detail for evaluation. Specify the type and number of subjects and how the data will be collected. Define the measurements, end points and the statistical protocols and analysis.

Protection of Human Subjects:

Data and Safety Monitoring Plan:

Use of Vertebrate Animals: Discuss how this model is relevant to hemorrhagic shock under combat conditions.

Provide a timetable for the proposed project:

Principal Investigator/Program Director (Last, First, Middle):

DETAILED COST ESTIMATE FOR INITIAL 12 MONTH BUDGET PERIOD (Direct costs only for applicant ORGANIZATION)					FROM	THROUGH	
PERSONNEL (<i>Applicant organization only</i>)		TYPE APPT. (months)	Institutional Annual Base Salary	% EFFORT ON PROJECT	DOLLAR AMOUNT REQUESTED (<i>omit cents</i>)		
NAME	ROLE ON PROJECT				SALARY REQUESTED	FRINGE BENEFITS	TOTAL
	Principal Investigator						
SUBTOTALS →							
CONSULTANT COSTS							
MAJOR EQUIPMENT (<i>Itemize</i>)							
MATERIALS, SUPPLIES AND CONSUMABLES (<i>Itemize by category</i>)							
TRAVEL COSTS							
RESEARCH-RELATED SUBJECT COSTS	INPATIENT						
	OUTPATIENT						
OTHER DIRECT COSTS (<i>Itemize by category</i>)							
CONSORTIUM/SUBAWARD - <u>DIRECT COSTS</u> **							
SUBTOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD (<i>Item 7a, Cover Page</i>) \$							
CONSORTIUM/SUBAWARD - <u>INDIRECT COSTS (FACILITIES/ADMINISTRATIVE COSTS)</u> **							
TOTAL DIRECT COSTS FOR INITIAL BUDGET PERIOD (<i>Item 7b, Cover Page</i>) \$							

***Include a separate Form of an initial 12 month budget for each consortium/subaward organization.*

Principal Investigator/Program Director (Last, First, Middle):

SUMMARY BUDGET FOR ENTIRE PROPOSED PERIOD OF SUPPORT <i>(Direct costs only for applicant organization)</i>			
BUDGET CATEGORY TOTALS	INITIAL BUDGET PERIOD (from Form D)	ADDITIONAL YEARS OF SUPPORT REQUESTED	
		2nd	3 rd (clinical only)
PERSONNEL: Salary and fringe benefits. Applicant organization only.			
CONSULTANT COSTS			
MAJOR EQUIPMENT			
MATERIALS, SUPPLIES AND CONSUMABLES			
TRAVEL COSTS			
RESEARCH-RELATED SUBJECT CARE COSTS	INPATIENT		
	OUTPATIENT		
OTHER EXPENSES			
CONSORTIUM/ SUBAWARD DIRECT COSTS **			
SUBTOTAL DIRECT COSTS PER YEAR			
SUBTOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT (Item 8a, Cover Page)			\$
CONSORTIUM/SUBAWARD INDIRECT COSTS ** (F&A)			
TOTAL DIRECT COSTS PER YEAR			
TOTAL DIRECT COSTS FOR ENTIRE PROPOSED PERIOD OF SUPPORT (Item 8b Cover Page)			\$
** Include a separate Form I for the entire proposed project period for each consortium/subaward organization.			
JUSTIFICATION. Use continuation pages as needed.			

Principal Investigator/Program Director (Last, First, Middle):

BIOGRAPHICAL SKETCH

Provide the following information for the key personnel and other significant contributors in the order listed on Form B. Follow this format for each person. **Do not exceed 3 pages per individual for full proposals or 2 pages for preproposals.**

NAME	POSITION TITLE		
EDUCATION/TRAINING <i>(Begin with baccalaureate or other initial professional education, such as nursing, and include postdoctoral training.)</i>			
INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	YEAR(s)	FIELD OF STUDY
RESEARCH AND PROFESSIONAL EXPERIENCE Positions and Honors. List in chronological order previous positions, concluding with your present position. List any honors. Include present membership on any Federal Government public advisory committee.			
Selected peer-reviewed publications (in chronological order). Do not cite manuscripts that are not yet accepted or published.			
Current research. List selected ongoing or completed (during the last three years) research projects. Begin with the projects that are most relevant to the research proposed in this application. Briefly indicate the overall goals of the projects and your role (e.g. PI, co-investigator, consultant) in the research project. Do not list award amounts or percent effort in projects.			

Principal Investigator/Program Director (Last, First, Middle):

AVAILABLE FACILITIES AND MAJOR EQUIPMENT

Describe the facilities available for performance of the proposed request and any additional facilities or equipment proposed for acquisition at no cost to USAMRMC. Indicate if government-owned facility or equipment is proposed for use. Reference should be made to the original or present contract under which the facilities or equipment items are now accountable.

FACILITIES: For each performance site identified on Form B, describe capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Under "Other," identify support services such as machine shop, electronics shop, and specify the extent to which they will be available to the project. Use continuation pages if necessary.

Laboratory:

Clinical:

Animal:

Computer:

Office:

Other:

MAJOR EQUIPMENT: List the most important equipment items already available for this project, noting the location and pertinent capabilities of each.

APPENDIX G. ACRONYMS AND GLOSSARY

G.1 Acronyms and Abbreviations

AFRRF	Advanced first-responder resuscitation fluid
AHA	American Heart Association
AMEDD C&S	Army Medical Department Center and School
BAA	Broad Agency Announcement
BLA	Biologic license application
CCCRP	Combat Casualty Care Research Program
CD	Compact disk
CG	Commanding General
CRADA	Cooperative Research and Development Agreement
DARPA	Defense Advanced Research Projects Agency
DCDD	Director of Combat and Doctrine Development
Deputy RM	Deputy Commander for Resource Management
Deputy R&T	Deputy Commander for Research and Technology
DHEA	Dehydroepiandrosterone
DOD	Department of Defense
DVD	Digital versatile disc
FDA	U.S. Food and Drug Administration
FOC	Full operational capability
HSD	Hypertonic saline dextran
IND	Investigational new drug
IOC	Initial operational capability
IP	Intellectual property
IPT	Integrated Project Team
J4 Med Rep	Joint Chiefs of Staff Logistics Directorate (J4) Medical Representative
LCM	Life Cycle Management
LD	Lethal dose
LSRO	Life Sciences Research Office, Inc.
MDA	Milestone Decision Authority
NAD(P)H	Nicotinamide-adenine dinucleotide phosphate
NDA	New drug application
NIH	National Institutes of Health
NHLBI	National Heart, Lung, and Blood Institute
NMRC	Naval Medical Research Center
OMR	Operations and Maintenance Appropriation
ONR	Office of Naval Research
PDF	Portable document format
PHS	Public Health Service
PULSE	Post-Resuscitative and Initial Utility in Life Saving Efforts
ROC	Resuscitation Outcomes Consortium
TBD	To be determined
TEMPOL	4-hydroxy-2,2,6,6-tetramethylpiperidine-1-oxyl
TRX	End of treatment
URL	Uniform resource locator
U.S.	United States
USAMMDA	U.S. Army Medical Materiel Development Activity
USAMRAA	U.S. Army Medical Research Acquisition Activity

USAMRMC U.S. Army Medical Research and Materiel Command
WG Work group
WRAIR Walter Reed Army Institute of Research

G.2 Glossary

Advanced trauma life support® A set of protocols published since 1980 by the American College of Surgeons for the physician who must effectively assess, initiate, and manage care for the patient with traumatic injury.

Casualty Combatant who has been physically injured.

Colloid intravenous fluid A fluid containing finely dispersed particles, such as starch, that are too large to readily pass through the capillary membrane. Colloid solutions are used to maintain fluid in the intravascular space.

Conflict-of-interest Conflict of interest and/or vested interests refers to personal and substantial participation in the study topic by reason of direct (personal) or indirect (*e.g.*, spouse, minor children, partner, immediate employer) control of financial interests affected by the nature of the study topic and/or the potential to benefit financially from regulatory or policy decisions of the study sponsor that result from conclusions, recommendations, or suggestions of the study report. Conflict of interest and vested interests also include contracts, consultancies, patents (issued or pending), or other legal arrangements with other agencies, organizations, and commercial firms (including employers) if such agreements or arrangements include the study topic under review.

Crystalloid intravenous fluid A solution of dissolved crystals, such as salts and sugars, that can pass through the capillary membrane into the tissue. Normal saline and lactated Ringer's are examples of crystalloid intravenous fluid.

Cytoprotector A class of pharmacologic agents that might improve the resistance of cells to necrosis and apoptosis through a variety of mechanisms, including antioxidation.

Echelon In a theatre of military operations, troops are organized in step-wise formations, categorized by level of echelon. The first echelon represents the unit support area encompassing the front-line, the second echelon corresponds to the brigade and divisional support areas, the third echelon represents the corps support areas, and the fourth echelon is the area that is most secure, outside the combat zone. Pre-hospital military care consists of two echelons of deployable medical facilities (Zajtchuk et al., 1991).

Far-forward A position within or near the battle area.

Fluid resuscitation Treatment regimen involving fluid replacement of lost blood volume, which is intended to minimize the effects of hemorrhagic shock and to stabilize the hemodynamic response to trauma and hypovolemia (Institute of Medicine, 1999).

Hextend® A 6% hetastarch resuscitation fluid containing salt solution (sodium, potassium, calcium, magnesium, chloride), glucose (90 mg/dL), and a lactate buffer.

Hydroxyethyl starch A derivative of amylopectin produced by introducing hydroxyethyl groups at three positions of glucose residues. The resulting product can vary in molecular weight, C₂/C₆ ratio, and function depending on the molar ratio of hydroxyethyl ether groups to glucose units (molar substitution).

Hypertonic saline A solution traditionally containing 3% or greater saline. Potential adverse effects include hypernatremia and hyperosmolar coma.

Hypertonic saline dextran (HSD) Solution containing 7.5% sodium chloride and 6% Dextran-70.

Hypovolemic shock Shock resulting from critical loss or redistribution of body fluid that severely comprises the ability of the heart to deliver blood for oxygenation of vital tissues. Severe internal or external hemorrhage can result in hypovolemic shock.

Killed-in-action (KIA) Casualties who die on the battlefield, such as the soldier who expires prior to reaching a battalion aide station or other medical treatment facility.

Lactated Ringer's solution A non-protein, non-carbohydrate isotonic crystalloid solution containing sodium chloride, sodium lactate, calcium chloride, and potassium chloride in distilled water. Synonym: Hartmann's solution.

Offeror An applicant who submits a preproposal or proposal to the military for potential funding.

Perfusion The act of pouring over or through, especially the passage of a fluid through the vessels of a specific organ.

Phase I clinical trials Development of a pharmacological profile on normal volunteers. Studies determine the metabolism, pharmacologic action, immunogenicity, and other biologic effects of a treatment, as well as safety, in a small number (20-80) of closely monitored human subjects.

Phase II clinical trials Pilot efficacy studies carefully controlled by experts to assess efficacy, preliminary safety profile, and minimum effective dose. The studies are designed to further confirm the safety and effectiveness of the treatment, including dose-response, for particular indications in patients with the disease or condition under study. Identifies common short-term side effects and risks and may compare the treatment to commonly used treatments. May enroll hundreds (100-300) of human subjects, often in randomized, placebo-controlled studies.

Phase III clinical trials Extensive clinical trials to confirm earlier efficacy studies beyond reasonable doubt and identify low incidence adverse reactions. Studies provide additional data on safety and effectiveness under prescribed use conditions over long-term periods by enrolling larger numbers of patients for greater duration than had been previously studied; may enroll thousands (1,000-3,000) of individuals.

Phase IV clinical trials A post-market study occurring after treatment has been licensed and marketed. Studies provide additional data on safety under conditions of actual usage by a broader spectrum of patients than had been previously studied in pre-market studies.

Preclinical Research that is theoretical or of basic science that precedes and lays the groundwork for a human clinical study. Preclinical *in vitro* and animal studies are used to generate hypotheses about the safety and efficacy of treatments that, with sufficient supporting data, are later tested in humans.

Pyrogenicity Characterizes the production of fever, as might occur in during an adverse reaction to an experimental product.

Resuscitation Outcomes Consortium (ROC) A consortium formed to test promising therapeutic strategies in multi-center trials in the areas of cardiopulmonary arrest and severe traumatic injury with a focus on interventions in the pre-hospital and early hospitalization phase of care (Resuscitation Outcomes Consortium, 2005).

Resuscitation science The study of the epidemiology, pathophysiology, mechanisms, and improved management of the sudden states of illness or injuries, which result in impending or actual cessation of oxygen delivery (Becker et al., 2002).

Rheology The study of the flow of matter, such as fluids and cells in the circulatory system.

Shock Condition of inadequate tissue perfusion and inadequate removal of cellular waste products, leading to subsequent failure of oxidative metabolism. Shock may result from deficits in (1) delivery, (2) transport, or (3) utilization of oxygen, or combinations of all three (Institute of Medicine, 1999).

G.3 Glossary Literature Citations

Becker, L. B., Weisfeldt, M. L., Weil, M. H., Budinger, T., Carrico, J., Kern, K., Nichol, G., Shechter, I., Traystman, R., Webb, C., Wiedemann, H., Wise, R. & Sopko, G. (2002) The PULSE initiative: scientific priorities and strategic planning for resuscitation research and life saving therapies. *Circulation* 105: 2562-2570.

Institute of Medicine (1999) Fluid Resuscitation. State of the Science for Treating Combat Casualties and Civilian Injuries. (Pope, A., French, G. & Longnecker, D. E., eds.) Washington, DC: National Academy Press.

Resuscitation Outcomes Consortium. (2005) Resuscitation Outcomes Consortium: Mission Statement. Available at <https://roc.uwctc.org/tiki/tiki-index.php>. Accessed 6-1-2005.

Zajtchuk, R., Jenkins, D. P., Bellamy, R. F., Quick, C. M., & Moore, C. C. (1991) Combat Casualty Care Guidelines: Operation Desert Storm. Available at <http://www.bordeninstitute.army.mil/cmbtcslycare/default.htm>. Accessed 11-17-2004.